“Neoplasias Mieloproliferativas *bcr-abl* negativas …

…más allá de JAK2”

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Introducción

- Antiguo grupo de enfermedades de difícil estudio, caracterizado por un incremento sostenido de la actividad de la línea mieloide, distinto de la Leucemia Mieloide Crónica (bcr-abl positiva) que se expresa en una proliferación celular desproporcionada y NO reactiva que se mantiene en el tiempo.
- Se agrupan tradicionalmente en este grupo a la Policitemia Rubra Vera, la Trombocitosis Esencial y la Mielofibrosis Primaria, entre otras patologías.

Introducción

- Enfermedades consideradas infrecuentes pero que han aumentado considerablemente en países desarrollados en atención a sus cambios demográficos.
- La Incidencia Acumulada en Suecia entre 1983 y 1992 fue de 2.8 por 100 000 h para la Policitemia Rubra Vera, de 1.5 para la trombocitosis esencial y de 0.4 para la Mielofibrosis primaria (Pathol Biol 2001 ; 49 : 164-6).
- En USA al 2003 había 65243 pacientes con PV y 71078 pacientes con ET (Am J Hematol. 2008 83(5):359-62).
- Para la mielofibrosis primaria la incidencia es menor : 3 a 15 por millón al año (USA).

Historia

- William Dameshek asocia enfermedades proliferativas “en masa” de la médula ósea bajo el concepto de “Sindromes Mieloproliferativos”.
- En 1967 Louis Wasserman reune un grupo multinacional de expertos en la materia y funda el “Polycythemia Vera Study Group (PVSG)” que establece criterios diagnósticos orientados fundamentalmente a la investigación.

TABLE 1.—*The Myeloproliferative Disorders*

Myelostimulatory Factor's) → Bone marrow → Potential bone marrow

Syndromes	Erythroblasts	Granulocytes	Megakaryocytes	Fibroblasts	Myeloid metaplasia of spleen and liver
Chronic Granulocytic Leukemia	±	+++	+ to +++	+	++
Polycythemia Vera	+++	++	++ to +++	+ to +++	+ to +++
Idiopathic or Agnogenic Myeloid Metaplasia of Spleen	±	±	+++	+ to +++	+++
Megakaryocytic Leukemia	±	±	+++	+	+ to +++
Erythroleukemia (including diGuglielmo syndrome)	+++	+	±	±	+ to +++

Degrees of Proliferation: + slight
++ moderate
+++ marked

Editorial : Some Speculations on the Myeloproliferative Syndromes

William Dameshek - Blood 1951 6: 372-375

Historia

- En 2001 la OMS establece un nuevo sistema de clasificación y diagnóstico, que busca aumentar la especificidad de éste último.
- En 2005 se publican con meses de diferencia distintos estudios clínicos relacionados con mutaciones de JAK 2, destacando la mutación 'activante' JAK2 V617F como un factor crucial en el desarrollo de estas enfermedades, destacandolas de Baxter et cols y de Kralovics et cols (Lancet 2005 365:1054-1061 ; NEJM 2005 352:1779-1790).

Historia

- En 2007 un panel de expertos propone a la OMS cambios importantes en su clasificación, de manera de incorporar en ella los hallazgos moleculares del último lustro.

  (Blood 2007 110: 1092-1097).

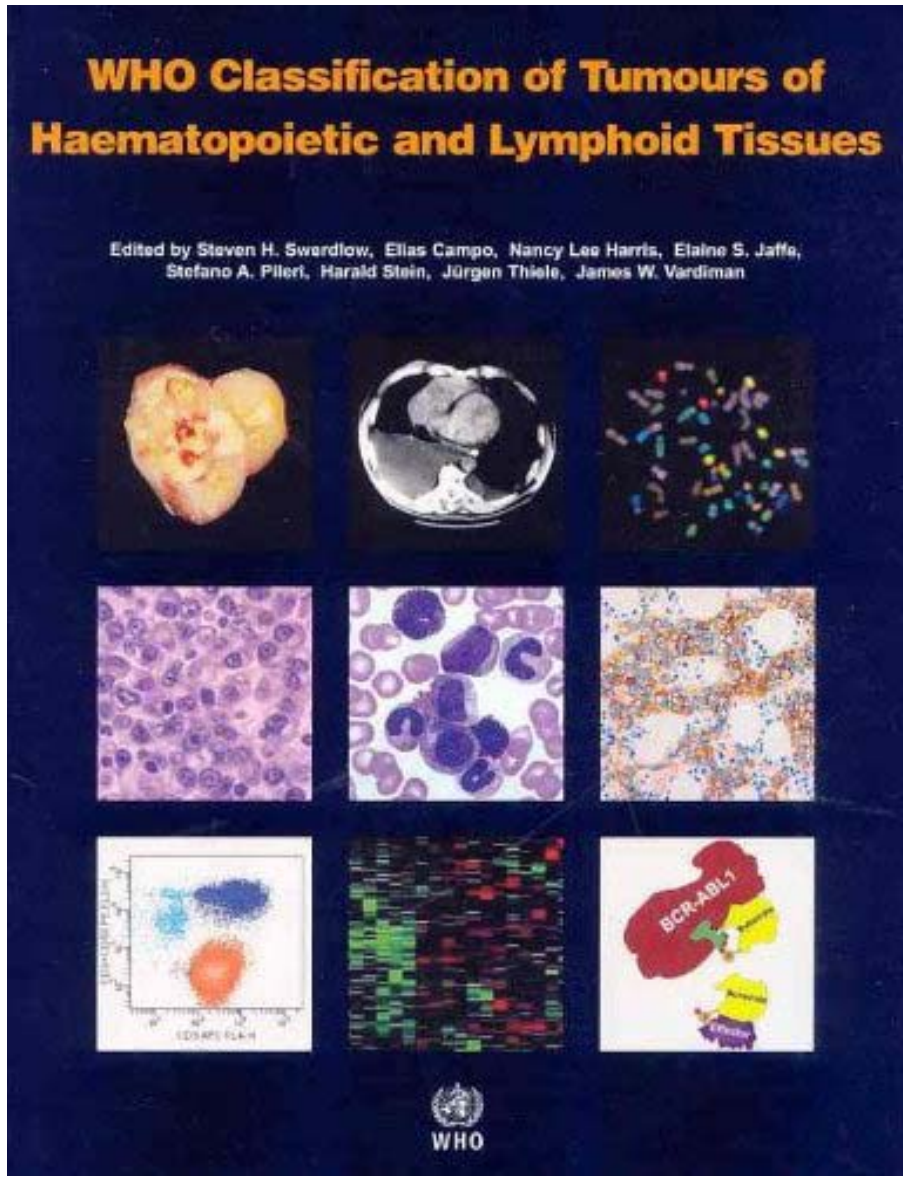
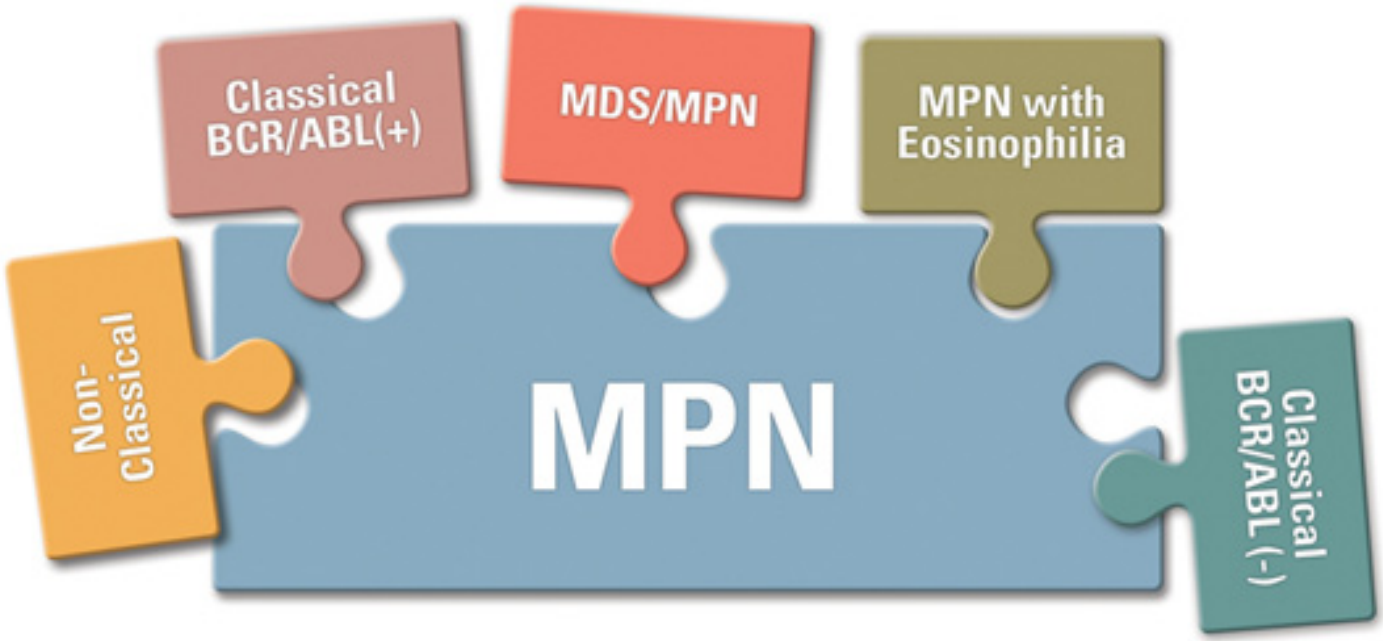


Table 1. Milestones in the History of Philadelphia-Negative Myeloproliferative Disorders and Their Relationship with the V617F Mutation in *JAK2*.*

Year	Historical Milestone	Relationship Later Established with V617F Mutation in *JAK2*
1892	First description of polycythemia vera[4]	
1951	Polycythemia vera, essential thrombocythemia, and idiopathic myelofibrosis linked as related conditions[5]	Mutation found in all three disorders[6-9]
1974	Identification of erythropoietin-independent erythroid colonies[10]	Mutation associated with cytokine independence of primary erythroid progenitors and cell lines[6-9]
1976	Stem-cell origin of polycythemia vera[11]	Mutation found in multipotent progenitors and hematopoietic stem cells[6,12]
1983–2003	Dysregulated tyrosine kinases found in chronic myeloid leukemia,[13,14] mastocytosis,[15] chronic myelomonocytic leukemia,[16,17] and chronic eosinophilic leukemia[18]	Tyrosine kinase function of JAK2 constitutively activated by mutation[7-9,19]
2002	Description of mitotic recombination involving chromosome 9p as the most common cytogenetic lesion in polycythemia vera[20]	Homozygosity of the mutation caused by mitotic recombination of chromosome 9p[6-9]
2001–2004	Erythropoietin-independent growth in polycythemia vera dependent on JAK–STAT signaling[21,22]	STAT proteins constitutively activated by mutation[7-9,19]
2005	Description of the *JAK2* V617F mutation[6-9,19]	

* STAT denotes signal transducers and activators of transcription.

Overwhelmed by the **WHO** Reclassification of Myeloproliferative Neoplasms (MPN) ?



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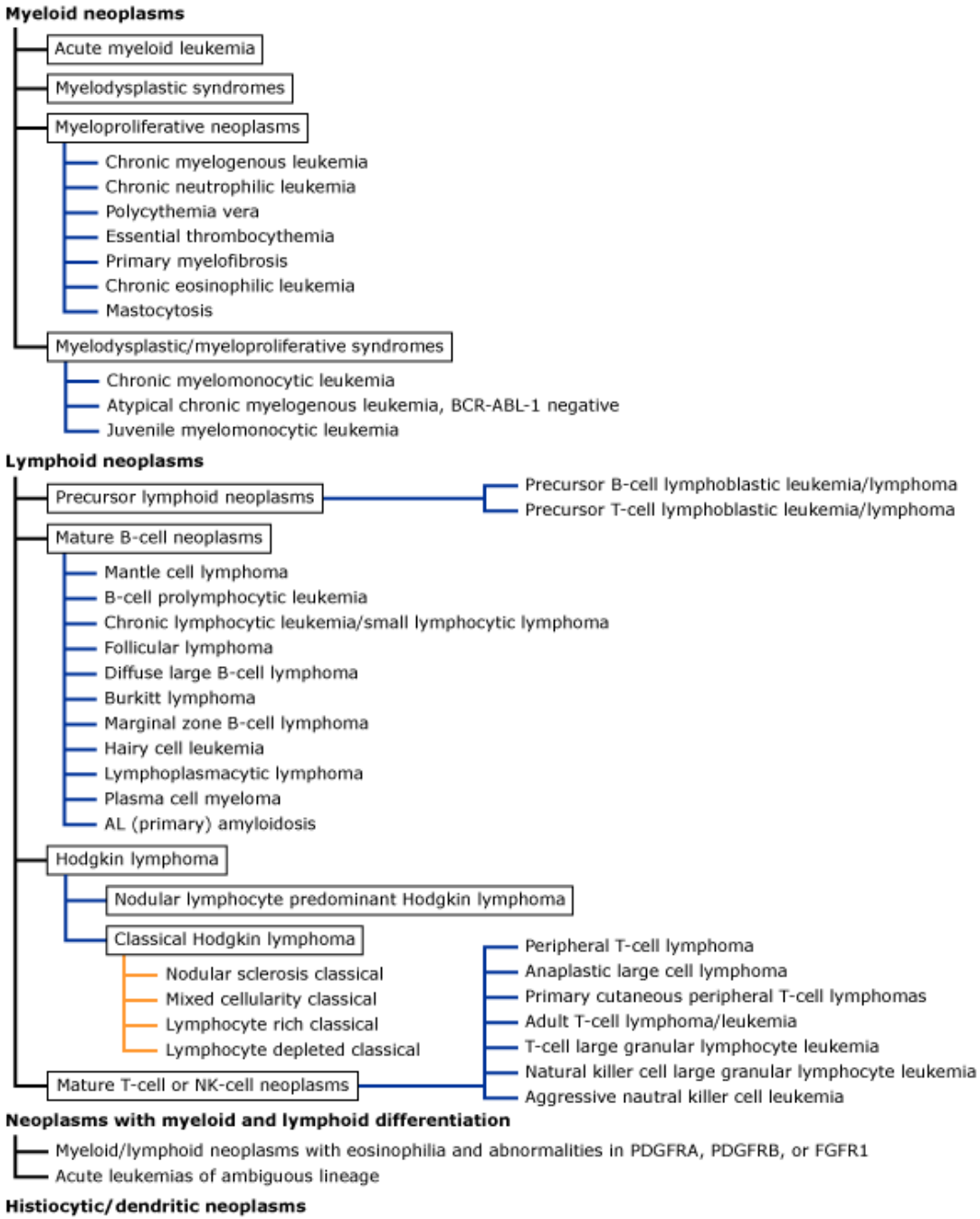
OMS 2008 – Un nuevo Orden



Clasificación OMS 2008

- En 2008 la OMS cambió la clasificación y los criterios diagnósticos :
- Se cambió el nombre del grupo a Neoplasias Mieloproliferativas.
- Se incluyó a este alero a la Leucemia Mieloide Crónica, a la PV, a la TE y la MFP, entre otras.
- Se excluyó del mismo a las neoplasias eosinofílicas con mutaciones conocidas.
- Se incorporó a las mutaciones de JAK2 como elemento central en el estudio diagnóstico, recomendando el estudio de exclusión fundamentalmente en los pacientes negativos para estas mutaciones.

Table 1. Classification of Myeloid Neoplasms According to the 2008 World Health Organization Classification Scheme

1. Myeloproliferative neoplasms (MPN)
- 1.1. Chronic myelogenous leukemia, *BCR-ABL1*–positive (CML)
- 1.2. Polycythemia vera (PV)
- 1.3. Essential thrombocythemia (ET)
- 1.4. Primary myelofibrosis (PMF)
- 1.5. Chronic neutrophilic leukemia (CNL)
- 1.6. Chronic eosinophilic leukemia, not otherwise specified (CEL-NOS)
- 1.7. Mast cell disease (MCD)
- 1.8. MPN, unclassifiable

2. Myeloid and lymphoid neoplasms with eosinophilia and abnormalities of *PDGFRA*, *PDGFRB*, and *FGFR1*

3. MDS/MPN
- 3.1. Chronic myelomonocytic leukemia (CMML)
- 3.2. Juvenile myelomonocytic leukemia (JMML)
- 3.3. Atypical chronic myeloid leukemia, *BCR-ABL*–negative (aCML)
- 3.4. MDS/MPN, unclassifiable

4. Myelodysplastic syndromes (MDS)

5. Acute myeloid leukemia (AML)

Table 1. 2001 WHO criteria for polycythemia vera

2001 criteria for PV
A-criteria
1. Elevated red cell mass > 25% above mean normal predicted value, or hemoglobin > 18.5 g/dL in men, 16.5 g/dL in women, or > 99th percentile of method-specific reference range for age, sex, altitude of residence
2. No cause of secondary erythrocytosis, including:
a. Absence of familial erythrocytosis
b. No elevation of erythropoietin caused by:
i. Hypoxia (arterial $pO_2 \leq 92\%$)
ii. High oxygen affinity hemoglobin
iii. Truncated erythropoietin receptor
iv. Inappropriate erythropoietin production by tumor
3. Splenomegaly
4. Clonal genetic abnormality other than Philadelphia chromosome or *BCR-ABL* fusion gene in marrow cells
5. Endogenous erythroid colony formation
B-criteria
1. Thrombocytosis > 400×10^9/L
2. Leukocytosis > 12×10^9/L
3. Bone marrow biopsy showing panmyelosis with prominent erythroid and megakaryocytic proliferation
4. Low serum erythropoietin levels

Diagnosis requires the presence of the first 2 A-criteria together with either any 1 other A-criterion or 2 B-criteria.

Table 2. Proposed revised WHO criteria for polycythemia vera

Proposed criteria for PV
Major criteria
1. Hemoglobin > 18.5 g/dL in men, 16.5 g/dL in women or other evidence of increased red cell volume*
2. Presence of *JAK2*617V>F or other functionally similar mutation such as *JAK2* exon 12 mutation
Minor criteria
1. Bone marrow biopsy showing hypercellularity for age with trilineage growth (panmyelosis) with prominent erythroid, granulocytic, and megakaryocytic proliferation
2. Serum erythropoietin level below the reference range for normal
3. Endogenous erythroid colony formation in vitro

Diagnosis requires the presence of both major criteria and 1 minor criterion or the presence of the first major criterion together with 2 minor criteria.

*Hemoglobin or hematocrit greater than 99th percentile of method-specific reference range for age, sex, altitude of residence or hemoglobin greater than 17 g/dL in men, 15 g/dL in women if associated with a documented and sustained increase of at least 2 g/dL from an individual's baseline value that can not be attributed to correction of iron deficiency, or elevated red cell mass greater than 25% above mean normal predicted value.

(Blood. 2007;110:1092-1097)

Table 3. 2001 World Health Organization criteria for essential thrombocythemia

2001 criteria for ET
Positive criteria
1. Sustained platelet count ≥ 600 × 10^9/L
2. Bone marrow biopsy specimen showing proliferation mainly of the megakaryocytic lineage with increased numbers of enlarged, mature megakaryocytes
Criteria of exclusion
1. No evidence of polycythemia vera
a. Normal red cell mass or hemoglobin < 18.5 g/dL in men, 16.5 g/dL in women
b. Stainable iron in marrow, normal serum ferritin, or normal MCV
c. If the former condition is not met, failure of iron trial to increase red cell mass or hemoglobin levels to the PV range
2. No evidence of chronic myeloid leukemia: no Philadelphia chromosome and no *BCR-ABL* fusion gene
3. No evidence of chronic idiopathic myelofibrosis
a. Collagen fibrosis absent
b. Reticulin fibrosis minimal or absent
4. No evidence of myelodysplastic syndrome
a. No del(5q), t(3;3)(q21;q26), inv(3)(q21q26)
b. No significant granulocytic dysplasia, few, if any, micromegakaryocytes
5. No evidence that thrombocytosis is reactive caused by
a. Underlying inflammation or infection
b. Underlying neoplasm
c. Prior splenectomy

Table 4. Proposed revised WHO criteria for essential thrombocythemia (ET)

Proposed criteria for ET
1. Sustained platelet count ≥ 450 × 10^9/L*
2. Bone marrow biopsy specimen showing proliferation mainly of the megakaryocytic lineage with increased numbers of enlarged, mature megakaryocytes; no significant increase or left-shift of neutrophil granulopoiesis or erythropoiesis
3. Not meeting WHO criteria for PV,† PMF,‡ CML,§ MDS,¶ or other myeloid neoplasm
4. Demonstration of *JAK2*617V>F or other clonal marker, or in the absence of a clonal marker, no evidence for reactive thrombocytosis‖

Diagnosis requires meeting all 4 criteria.

* During the work-up period.

† Requires the failure of iron replacement therapy to increase hemoglobin level to the PV range in the presence of decreased serum ferritin. Exclusion of PV is based on hemoglobin and hematocrit levels, and red cell mass measurement is not required.

‡ Requires the absence of relevant reticulin fibrosis, collagen fibrosis, peripheral blood leukoerythroblastosis, or markedly hypercellular marrow for age accompanied by megakaryocyte morphology that is typical for PMF– small to large with an aberrant nuclear/cytoplasmic ratio and hyperchromatic, bulbous or irregularly folded nuclei and dense clustering.

§ Requires the absence of *BCR-ABL*.

¶ Requires absence of dyserythropoiesis and dysgranulopoiesis.

‖ Causes of reactive thrombocytosis include iron deficiency, splenectomy, surgery, infection, inflammation, connective tissue disease, metastatic cancer, and lymphoproliferative disorders. However, the presence of a condition associated with reactive thrombocytosis does not exclude the possibility of ET if the first three criteria are met.

(Blood. 2007;110:1092-1097)

Table 5. 2001 WHO criteria for prefibrotic stage primary myelofibrosis

2001 criteria for prefibrotic PMF
Clinical findings
Spleen and liver
No or mild splenomegaly or hepatomegaly
Hematology (variable)
Mild anemia
Mild to moderate leukocytosis
Mild to marked thrombocytosis
Morphological findings
Blood
No or mild leukoerythroblastosis
No or mild red blood cell poikilocytosis
Few if any dacryocytes
Bone marrow
Hypercellularity
Neutrophilic proliferation
Megakaryocytic proliferation
Megakaryocytic atypia*
Minimal or absent reticulin fibrosis

*Clustering of megakaryocytes, abnormally lobulated megakaryocytic nuclei, naked megakaryocytic nuclei.

Table 6. 2001 WHO criteria for fibrotic stage primary myelofibrosis

2001 criteria for fibrotic PMF
Clinical findings
Spleen and liver
Moderate to marked splenomegaly or hepatomegaly
Hematology
Moderate to marked anemia
White blood cells decreased to elevated
Platelet count decreased to elevated
Morphological findings
Blood
Leukoerythroblastosis
Prominent red blood cell poikilocytosis
Prominent dacryocytosis
Bone marrow
Reticulin and/or collagen fibrosis
Decreased cellularity
Dilated marrow sinuses
Intraluminal hematopoiesis
Neutrophilic proliferation
Prominent megakaryocytic proliferation
Megakaryocytic atypia*
New bone formation (osteosclerosis)

*Clustering of megakaryocytes, abnormally lobulated megakaryocytic nuclei, naked megakaryocytic nuclei.

(Blood. 2007;110:1092-1097)

Table 7. Proposed revised WHO criteria for primary myelofibrosis

Proposed criteria for PMF
Major criteria
1. Presence of megakaryocyte proliferation and atypia,* usually accompanied by either reticulin and/or collagen fibrosis, or, in the absence of significant reticulin fibrosis, the megakaryocyte changes must be accompanied by an increased bone marrow cellularity characterized by granulocytic proliferation and often decreased erythropoiesis (ie, prefibrotic cellular-phase disease)
2. Not meeting WHO criteria for PV,† CML,‡ MDS,§ or other myeloid neoplasm
3. Demonstration of *JAK2*617V>F or other clonal marker (eg, *MPL*515W>L/K), or in the absence of a clonal marker, no evidence of bone marrow fibrosis due to underlying inflammatory or other neoplastic diseases¶
Minor criteria
1. Leukoerythroblastosis‖
2. Increase in serum lactate dehydrogenase level‖
3. Anemia‖
4. Palpable splenomegaly‖

Diagnosis requires meeting all 3 major criteria and 2 minor criteria.

* Small to large megakaryocytes with an aberrant nuclear/cytoplasmic ratio and hyperchromatic, bulbous, or irregularly folded nuclei and dense clustering.

† Requires the failure of iron replacement therapy to increase hemoglobin level to the polycythemia vera range in the presence of decreased serum ferritin. Exclusion of polycythemia vera is based on hemoglobin and hematocrit levels. Red cell mass measurement is not required.

‡ Requires the absence of *BCR-ABL*.

§ Requires the absence of dyserythropoiesis and dysgranulopoiesis.

¶ Secondary to infection, autoimmune disorder or other chronic inflammatory condition, hairy cell leukemia or other lymphoid neoplasm, metastatic malignancy, or toxic (chronic) myelopathies. It should be noted that patients with conditions associated with reactive myelofibrosis are not immune to primary myelofibrosis and the diagnosis should be considered in such cases if other criteria are met,

‖ Degree of abnormality could be borderline or marked.

(Blood. 2007;110:1092-1097)

OMS – Criterios Diagnósticos

Table 2. The 2008 World Health Organization Diagnostic Criteria for Polycythemia Vera, Essential Thrombocythemia, and Primary Myelofibrosis[20]

2008 WHO Diagnostic Criteria

		PV*		ET†		PMF‡
Major criteria	1	Hgb >18.5 g/dL (men) >16.5 g/dL (women) or Hgb >17 g/dL (men), or >15 g/dL (women) if associated with a sustained increase of ≥2 g/dL from baseline that can not be attributed to correction of iron deficiency or§	1	Platelet count ≥450 × 10^9/L	1	Megakaryocyte proliferation and atypia‖ accompanied by either reticulin and/or collagen fibrosis, or In the absence of reticulin fibrosis, the megakaryocyte changes must be accompanied by increased bone marrow cellularity, granulocytic proliferation and often decreased erythropoiesis (ie, prefibrotic PMF).
	2	Presence of *JAK2*V617F or similar mutation	2	Megakaryocyte proliferation with large and mature morphology. No or little granulocyte or erythroid proliferation	2	Not meeting WHO criteria for CML, PV, MDS, or other myeloid neoplasm
			3	Not meeting WHO criteria for CML, PV, PMF, MDS or other myeloid neoplasm	3	Demonstration of *JAK2*V617F or other clonal marker or no evidence of reactive bone marrow fibrosis
			4	Demonstration of *JAK2*V617F or other clonal marker or no evidence of reactive thrombocytosis		
Minor criteria	1	BM trilineage myeloproliferation			1	Leukoerythroblastosis
	2	Subnormal serum Epo level			2	Increased serum LDH
	3	EEC growth			3	Anemia
					4	Palpable splenomegaly

WHO indicates World Health Organization; PV, polycythemia vera; ET, essential thrombocythemia; PMF, primary myelofibrosis; Hgb, hemoglobin; CML, chronic myelogenous leukemia; MDS, myelodysplastic syndrome; BM, bone marrow; Epo, erythropoietin; LDH, lactate dehydrogenase; EEC, endogenous erythroid colony.

*The diagnosis of PV requires meeting either both major criteria and 1 minor criterion or the first major criterion and 2 minor criteria.

†The diagnosis of ET requires meeting all 4 major criteria.

‡The diagnosis of PMF requires meeting all 3 major criteria and 2 minor criteria.

§Or Hgb or hematocrit greater than the 99th percentile of reference range for age, sex, or altitude of residence or red cell mass >25% above the mean normal predicted.

‖Small to large megakaryocytes with an aberrant nuclear/cytoplasmic ratio and hyperchromatic and irregularly folded nuclei and dense clustering.

Criterios de Transformación a Mielofibrosis

International Myelofibrosis Working Group

Tomado de " Philadelphia Chromosome–Negative Chronic Myeloproliferative Disease"
Juergen Thiele, MD - Am J Clin Pathol 2009;132:261-280

Table 3
Criteria for Post–Polycythemia Vera Myelofibrosis as Proposed by the International Myelofibrosis Working Group[104]

Required criteria
1. Documentation of a previous diagnosis of polycythemia vera as defined by the World Health Organization criteria
2. Bone marrow fibrosis grade 2 or 3 (on 0-3 scale)[78] or grade 3 or 4 (on 0-4 scale)[105]

Additional criteria (2 are required)
1. Anemia or sustained loss of requirement of phlebotomy (in the absence of cytoreductive therapy) or cytoreductive treatment for erythrocytosis
2. A leukoerythroblastic peripheral blood picture
3. Increasing splenomegaly defined as an increase in palpable splenomegaly of ≥5 cm (distance of the tip of the spleen from the left costal margin) or the appearance of a newly palpable splenomegaly
4. Development of ≥1 of 3 constitutional symptoms: >10% weight loss in 6 mo, night sweats, unexplained fever (>37.5°C)

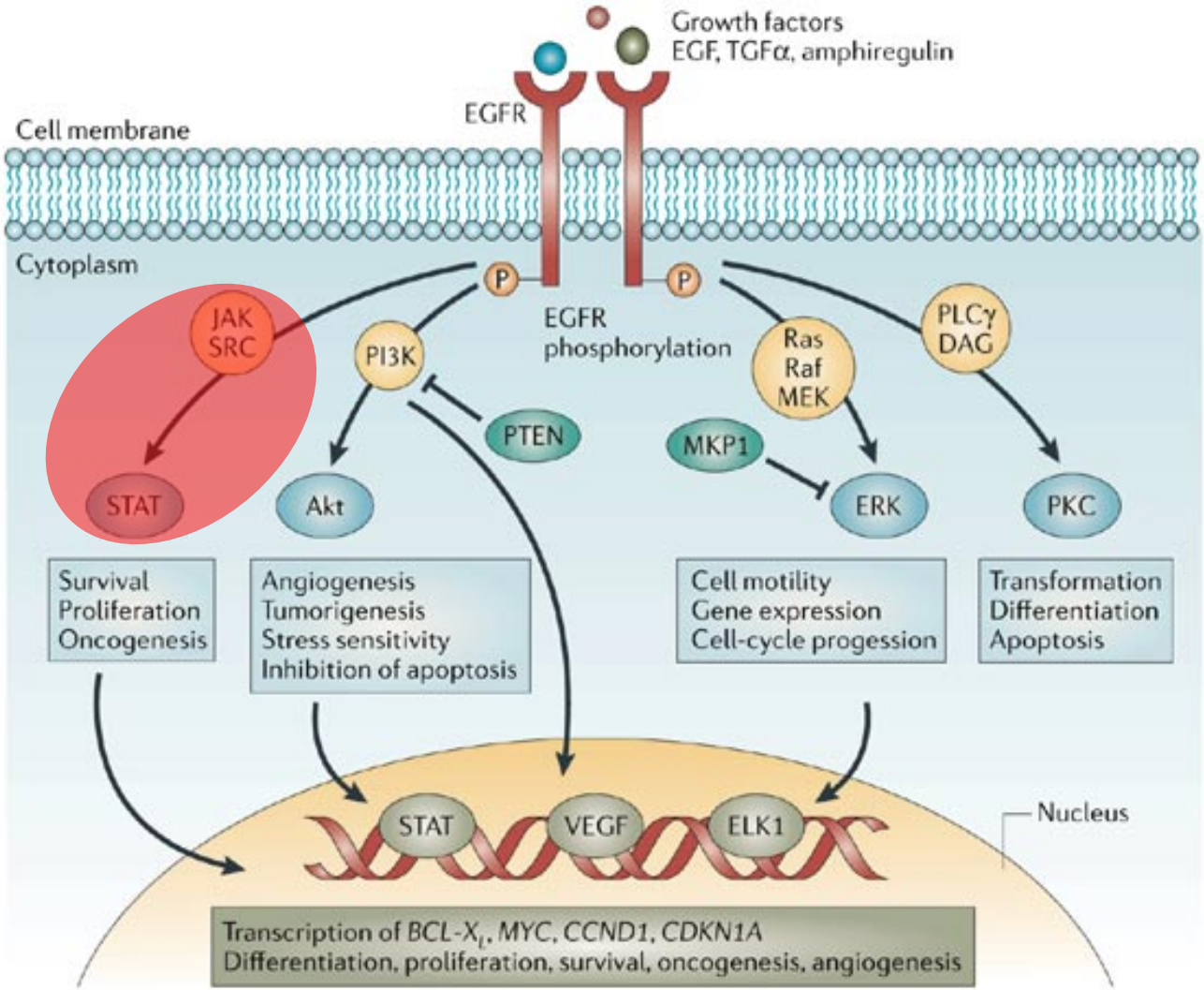
Table 4
Criteria for Post–Essential Thrombocythemia Myelofibrosis as Proposed by the International Myelofibrosis Working Group[104]

Required criteria
1. Documentation of a previous diagnosis of essential thrombocythemia as defined by the World Health Organization criteria
2. Bone marrow fibrosis grade 2 or 3 (on 0-3 scale)[78] or grade 3 or 4 (on 0-4 scale)[105]

Additional criteria (2 are required)
1. Anemia or a ≥2-g/dL decrease from baseline hemoglobin level
2. A leukoerythroblastic peripheral blood picture
3. Increasing splenomegaly defined as an increase in palpable splenomegaly of ≥5 cm (distance of the tip of the spleen from the left costal margin) or the appearance of a newly palpable splenomegaly
4. Increased lactate dehydrogenase level (above reference level)
5. Development of ≥1 of 3 constitutional symptoms: >10% weight loss in 6 mo, night sweats, unexplained fever (>37.5°C)

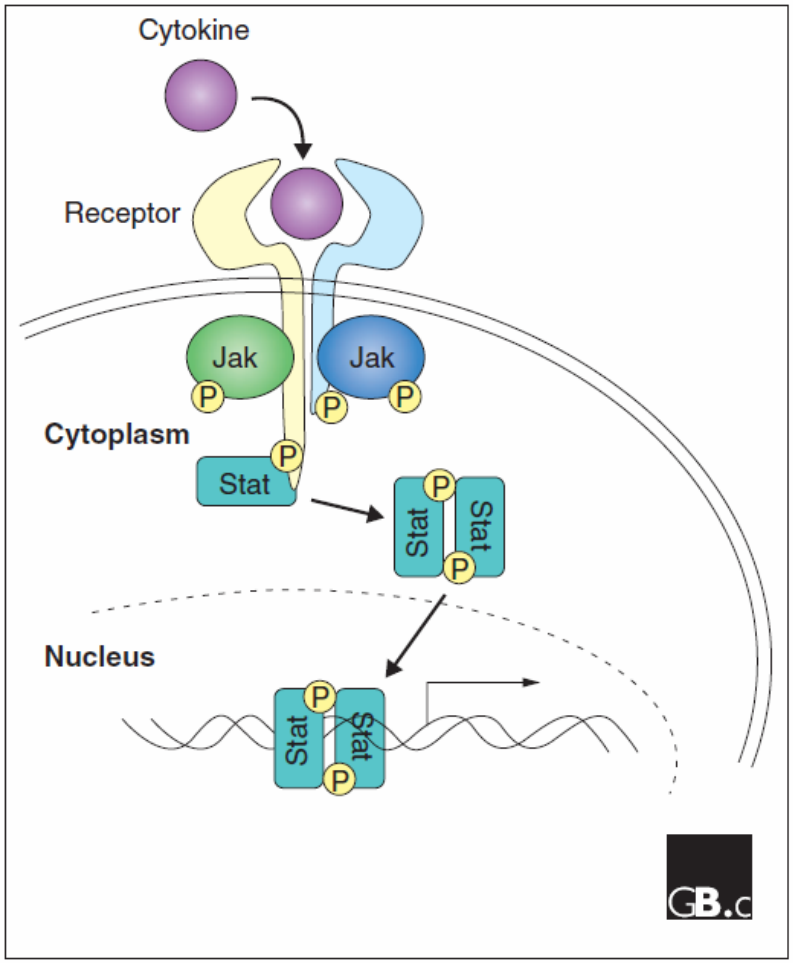
Janus de Roquepertuse, Francia

Biología Molecular de las Neoplasias Mieloproliferativas *bcr-abl* negativas



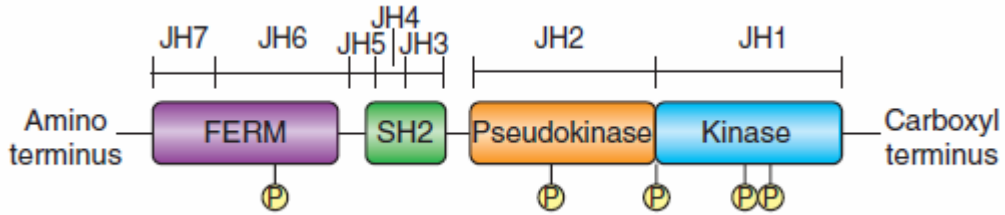
The main downstream signalling pathways regulated by GFR

Nature Reviews Cancer 6, 876-885 (November 2006)



An overview of cytokine signaling. Cytokines bind to homodimeric or heterodimeric receptors, which are constitutively bound to Jaks. Jaks are thought to be activated by a conformational change in the receptor that allows trans- and/or auto-phosphorylation of the two bound Jaks. These in turn phosphorylate the cytokine receptors. Stat proteins bind the phosphorylated receptor chains, allowing the Jaks to phosphorylate the Stats. Phosphorylated Stats form dimers and translocate and accumulate in the nucleus, where they regulate gene expression.

Genome ***Biology*** 2004, **5**:253



A schematic representation of the primary structure of Janus kinases (Jaks), which are made up of FERM, SH2-like, pseudokinase and kinase domains. An alternative nomenclature for the putative domains is as a series of Janus homology (JH) domains. The FERM domain mediates binding to cytokine receptors. Both the FERM and the pseudokinase domains regulate catalytic activity and appear to interact with the kinase domain. Jaks autophosphorylate at multiple sites (P), including two in the activation loop of the kinase domain, but the precise function of these modifications is just beginning to be understood.

Table 1

Functions of Jaks

Gene	Phenotype of mouse knockout	Cytokines whose signaling requires this Jak
Jak1	Viable but early postnatal lethal owing to neurological deficits; SCID	Families of receptor with the shared subunits γc or gp130; IFNs
Jak2	Embryonic lethal owing to a defect of erythropoiesis	IL-3; family of receptors with the shared subunit gp130; IFN-γ; hormone-like cytokines (EPO, GH, PRL, TPO)
Jak3	SCID, viable and fertile	Family of receptor with the shared subunit γc
Tyk2	Viable and fertile; susceptible to parasite infection; resistant to LPS; resistant to collagen-induced arthritis	IL-12; LPS

Abbreviations: EPO, erythropoietin; γc, common γ chain; GH, growth hormone; IFN, interferon; IL, interleukin; LPS, bacterial lipopolysaccharide; PRL, prolactin; SCID, severe combined immunodeficiency; TPO, thrombopoietin.

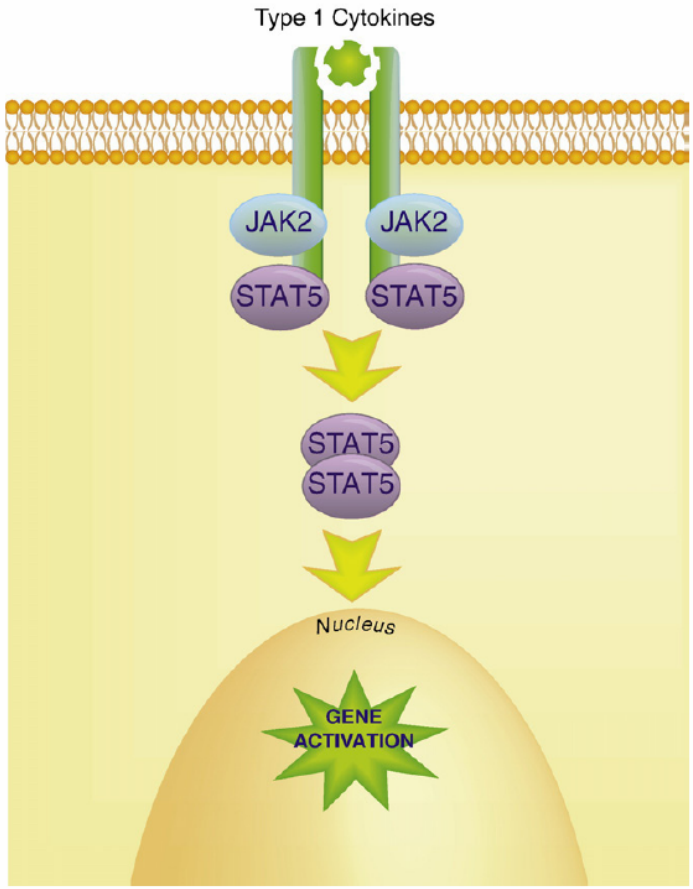


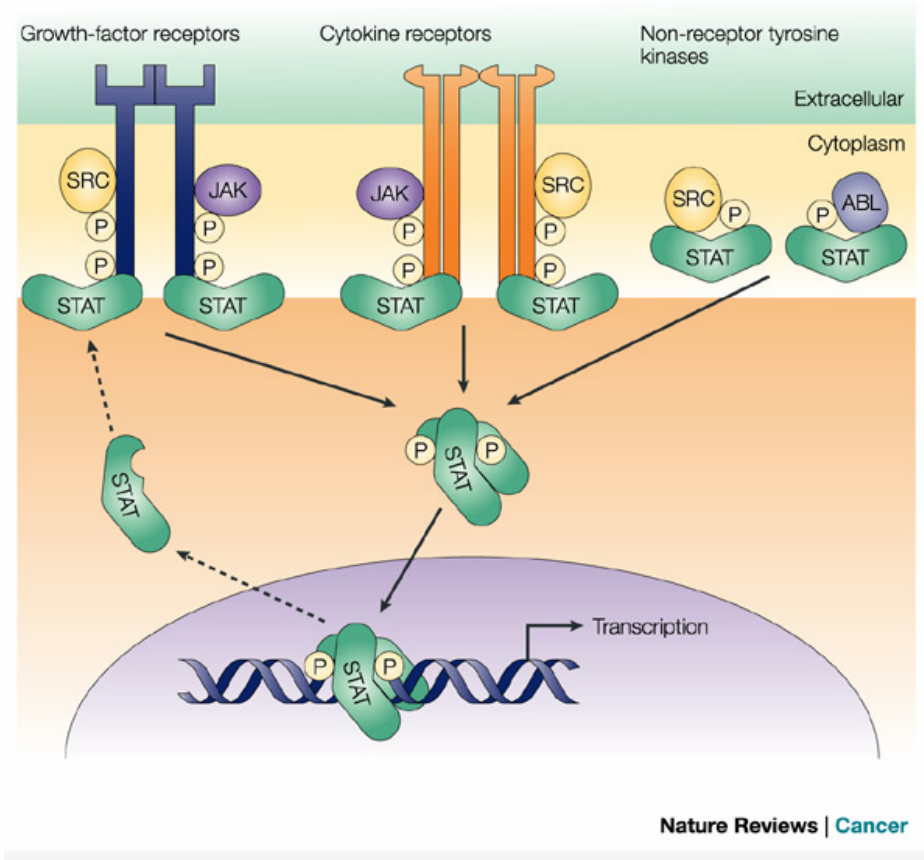
Fig. 2 JAK2 in type I cytokine signaling pathway. The binding of a ligand with type I cytokine receptor induces a conformational change in the receptor, bringing 2 JAK2 proteins close enough to phosphorylate each other. Phosphorylated JAK2 acts as an activated tyrosine kinase, phosphorylating the cytoplasmic domain of the type I cytokine receptors, which become the docking site of STAT proteins. When STAT proteins are bound to phosphorylated cytoplasmic domains of type I cytokine receptors, they are also phosphorylated by activated JAK2. The activated STATs form dimers and enter the nucleus, where they act as transcription factors to regulate the target gene.

Table 2. Stats in hematopoiesis: phenotypes of mouse knockouts

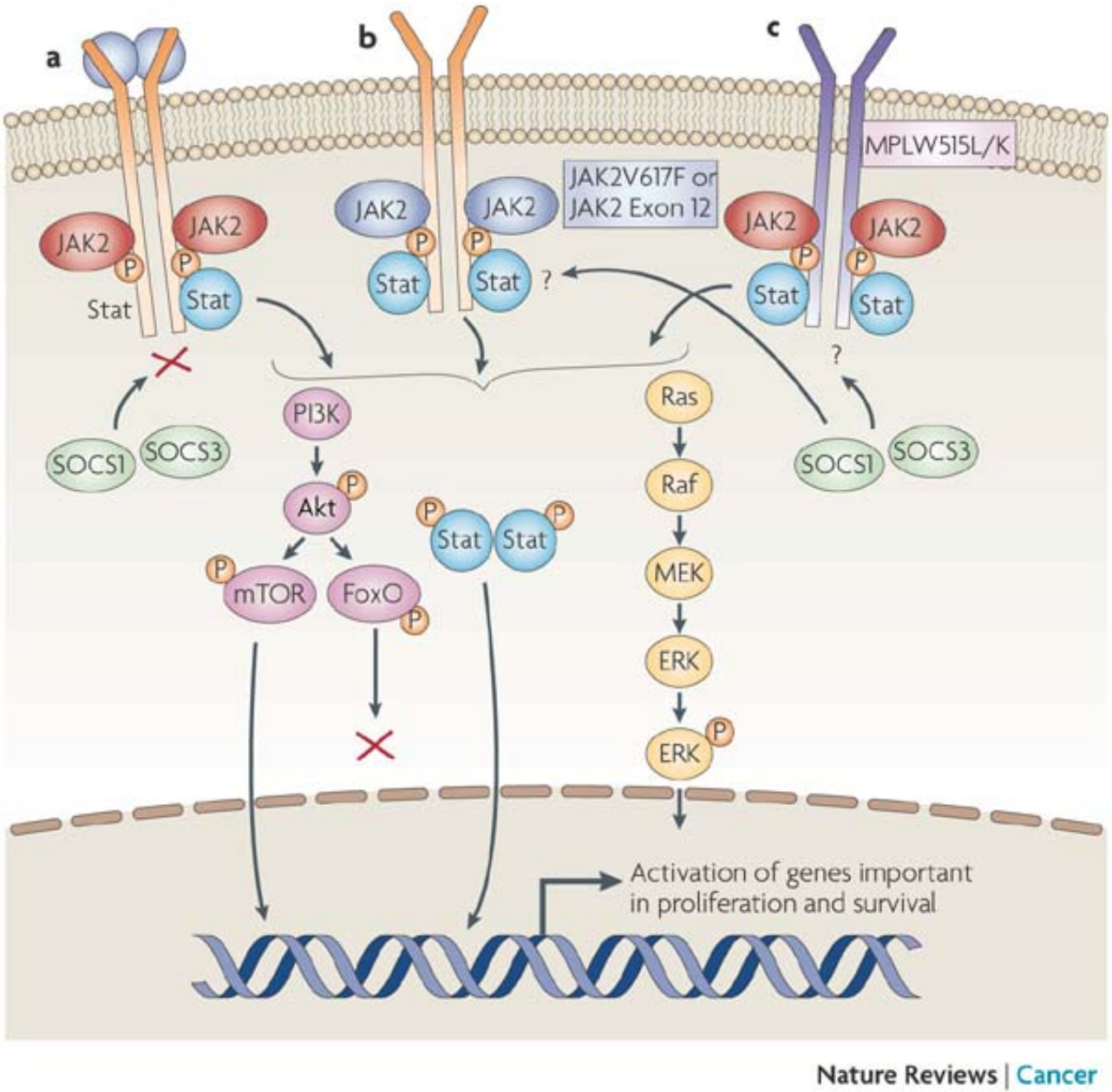
Stat Type	Relevant Phenotypes	Cytokines Affected	Refs
Stat1	• Interferon responses absent: —innate immune responses absent —highly sensitive to viral/microbial infection —IFN-responsive genes not activated	IFNs only	22, 23
Stat 2	• Type 1 interferon responses impaired	IFN-α/β	C. Schindler, pers. comm.
Stat 3	• Embryonic lethal		24
Stat 4	• IL-12 responses absent ↓ production of high IFN-γ, low IFN-γ Rα Th1 cells ↓ priming for high level IFN-γ production ↓ lymphocyte proliferation ↓ enhancement of NK cell-mediated cytotoxicity ↑ Th2 cells	IL-12 only	26, 27
Stat5ab	• Proliferation signaling affected: ↓ CFU-Mix, Eos, G, GM, Pre-B ↓ peripheral T cells Absence of NK cells	IL-2, IL-3, IL-7, GM-CSF, G-CSF	28, 29
Stat6	• IL-4 responses absent: -Absence of IL-4 producing Th2 cells -Block in B-cell IgE class switching ↓ lymphocyte proliferation (partial) ↓ expression of IL-4-induced cell surface markers	IL-4 only	32, 33, 179

CFU, colony-forming unit: G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; IFN, interferon; IL, interleukin; NK, natural killer.

BLOOD, 1 JANUARY 2000 • VOLUME 95, NUMBER 1



Nature Reviews Cancer 4, 97-105 (February 2004)



Mechanism of activation of JAK2 kinase activity by mutations in the JAK2 signalling pathway.

Nature Reviews Cancer 7, 673-683 (September 2007)

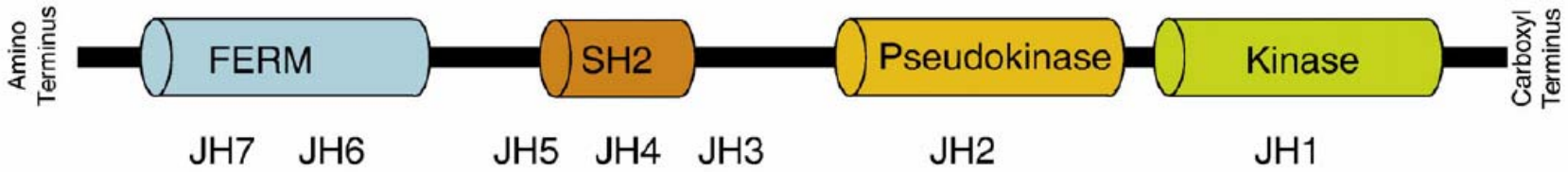


Fig. 1 The molecular structure of JAK2. JH1: active kinase domain with tyrosine residues. JH2: kinase-like domain. JH3 and JH4: Src homology region 2 (SH2) motif. JH5 through JH7: FERM (F for 4.1 protein, E for ezrin, R for radixin, and M for moesin) homology domain.

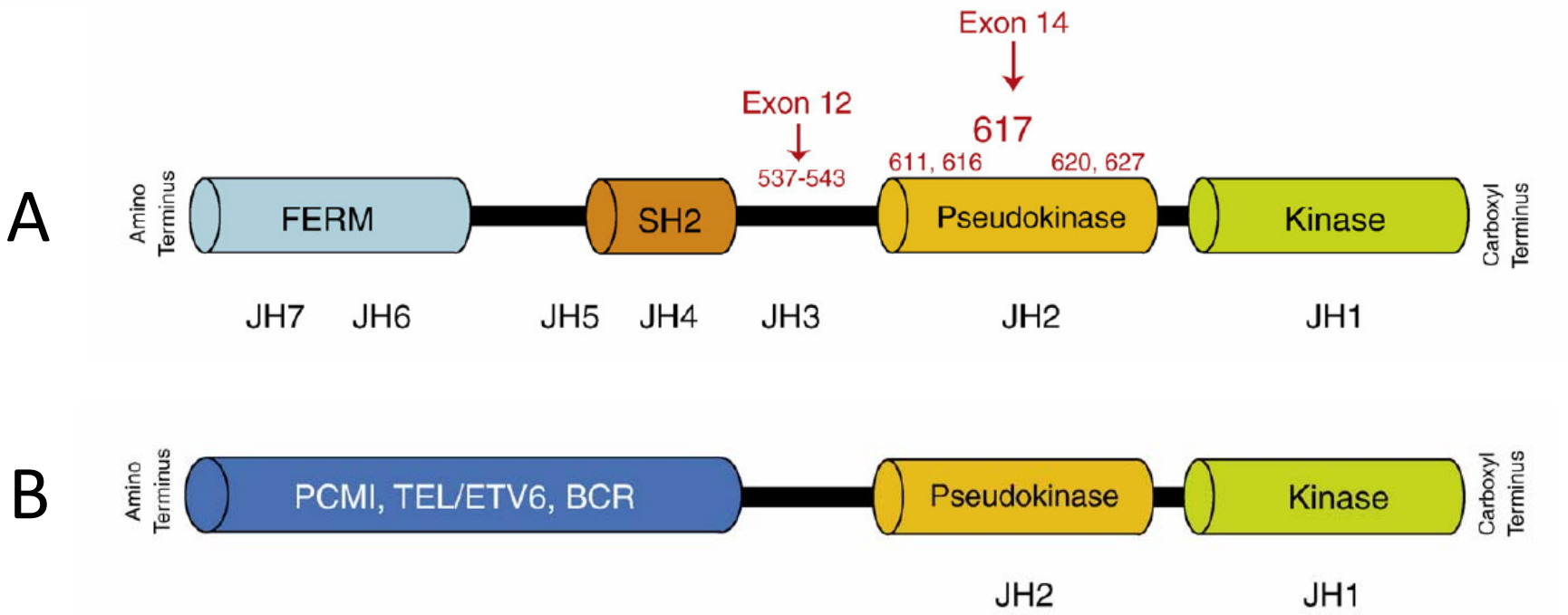
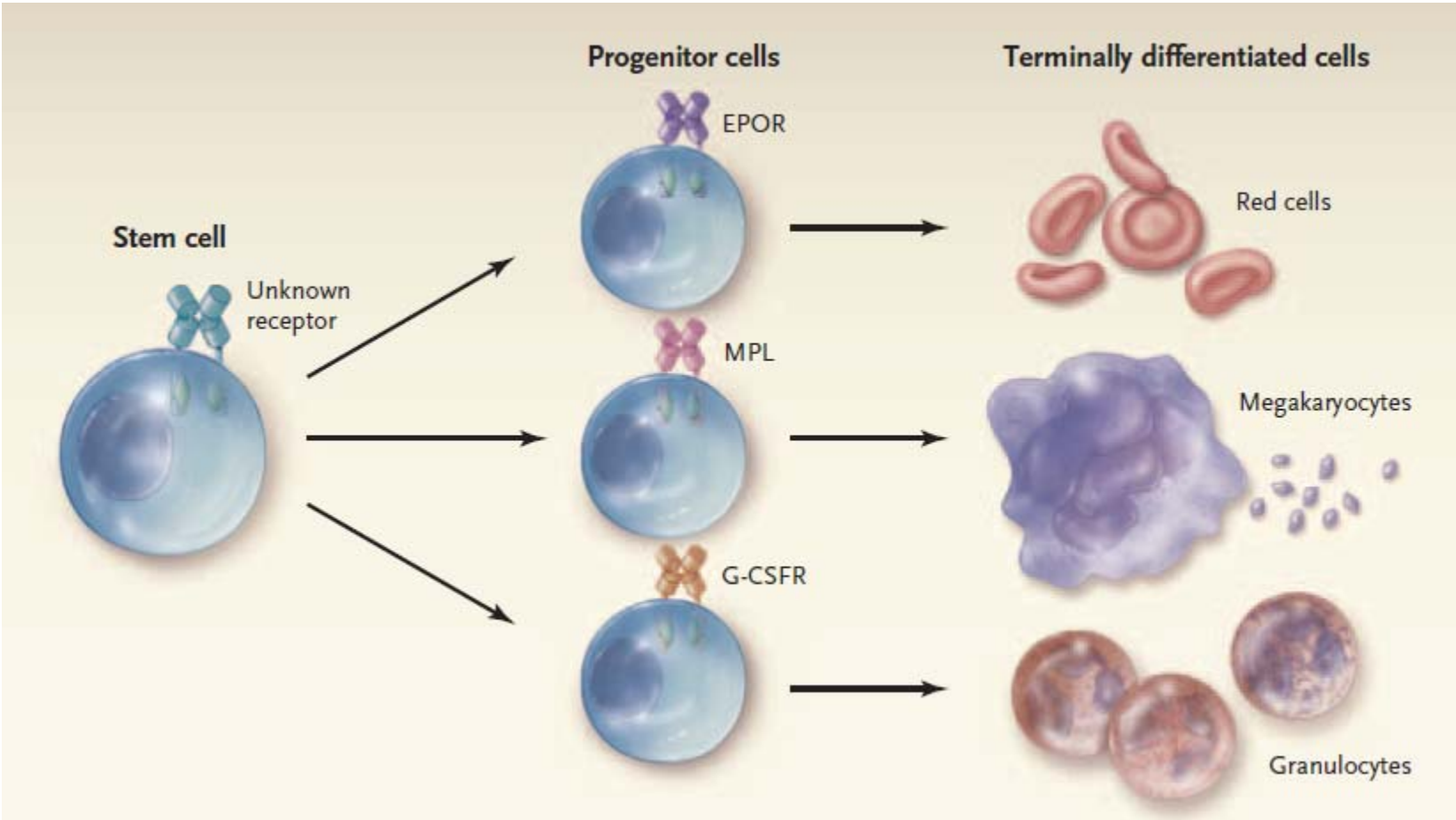


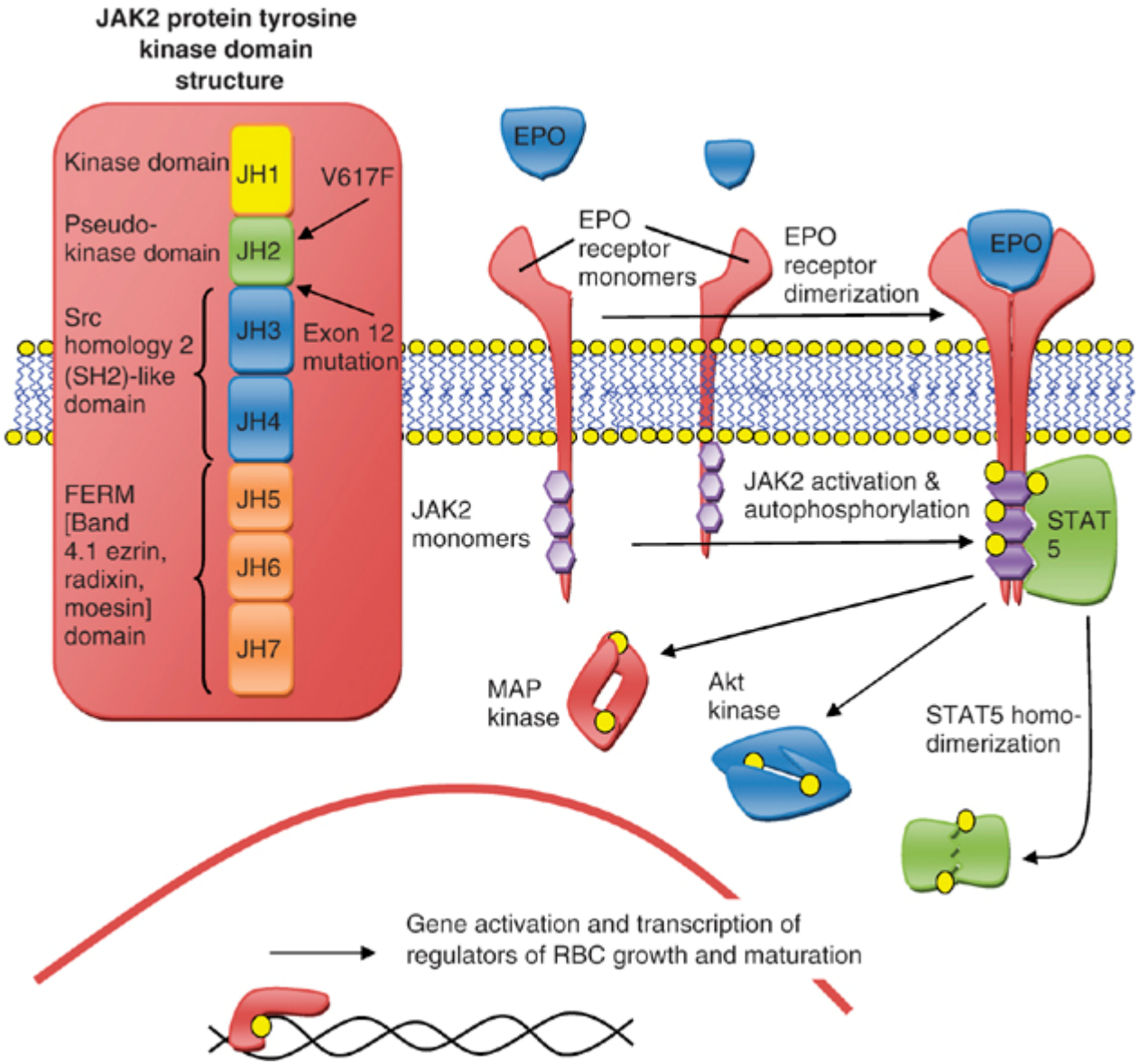
Fig. 3 JAK2 mutations and translocations. A, JAK2 point mutations and deletions implicated in MPN and acute leukemias are mainly located on exon 14 and 12. Exon 14 is the location of the JAK2V617F mutation and other mutations such as 611, 616, 620, and 627 mutations. Exon 12 mutations are clustered in 537 to 543. B, JAK2 fusion genes involved in myeloid and lymphoid leukemias include PCM1-JAK2, BCR-JAK2, and TEL/ETV6-JAK2. PCM1, TEL/ETV6, and BCR are fused to JH1 and/or JH2 domains of JAK2, providing a dimerization interface to the JAK2 kinase domain. PCM1-JAK2 was found in MPN and AML. BCR-JAK2 fusion was detected in aCML. TEL/ETV6-JAK2 fusion gene was identified in T-ALL, B-ALL, and aCML.



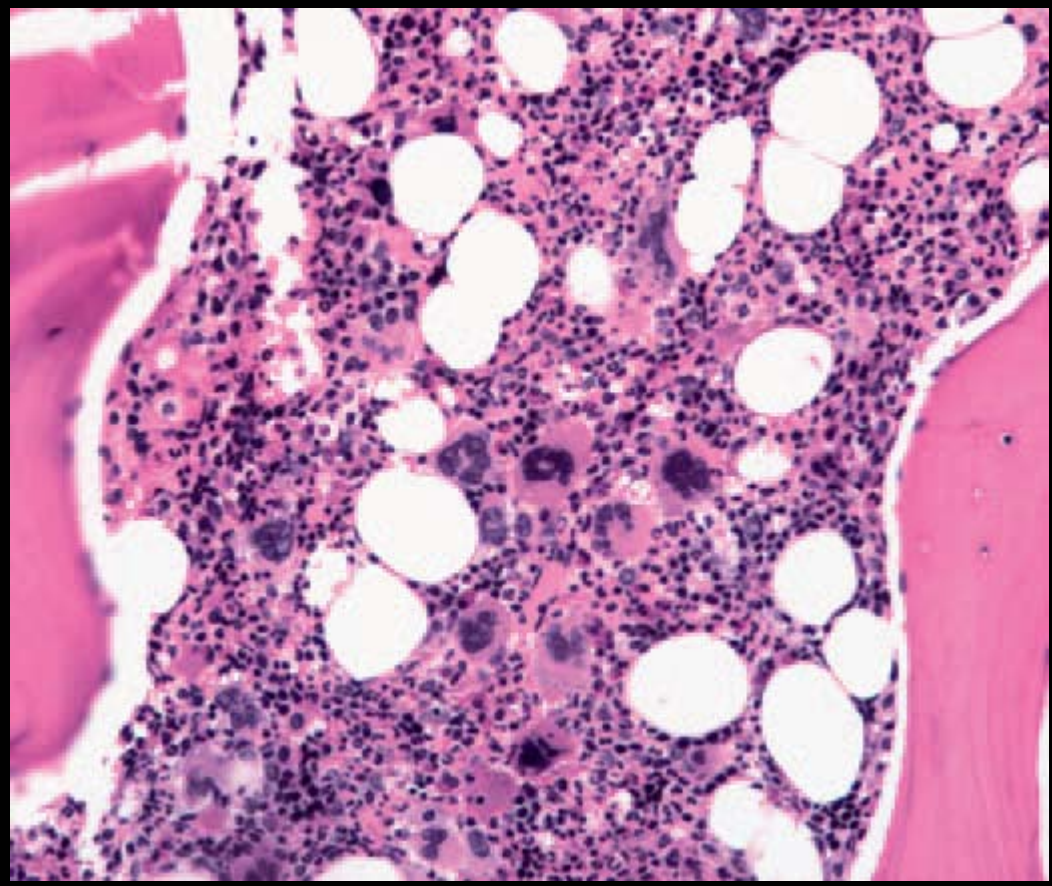
Dependiendo de la célula (receptor) y del ligando presente la actividad de JAK2 “wild type” genera el fenotipo celular, sean eritrocitos, magacariocitos o granulocitos a partir de la Stem Cell.

N Engl J Med 2006;355:2452-66.

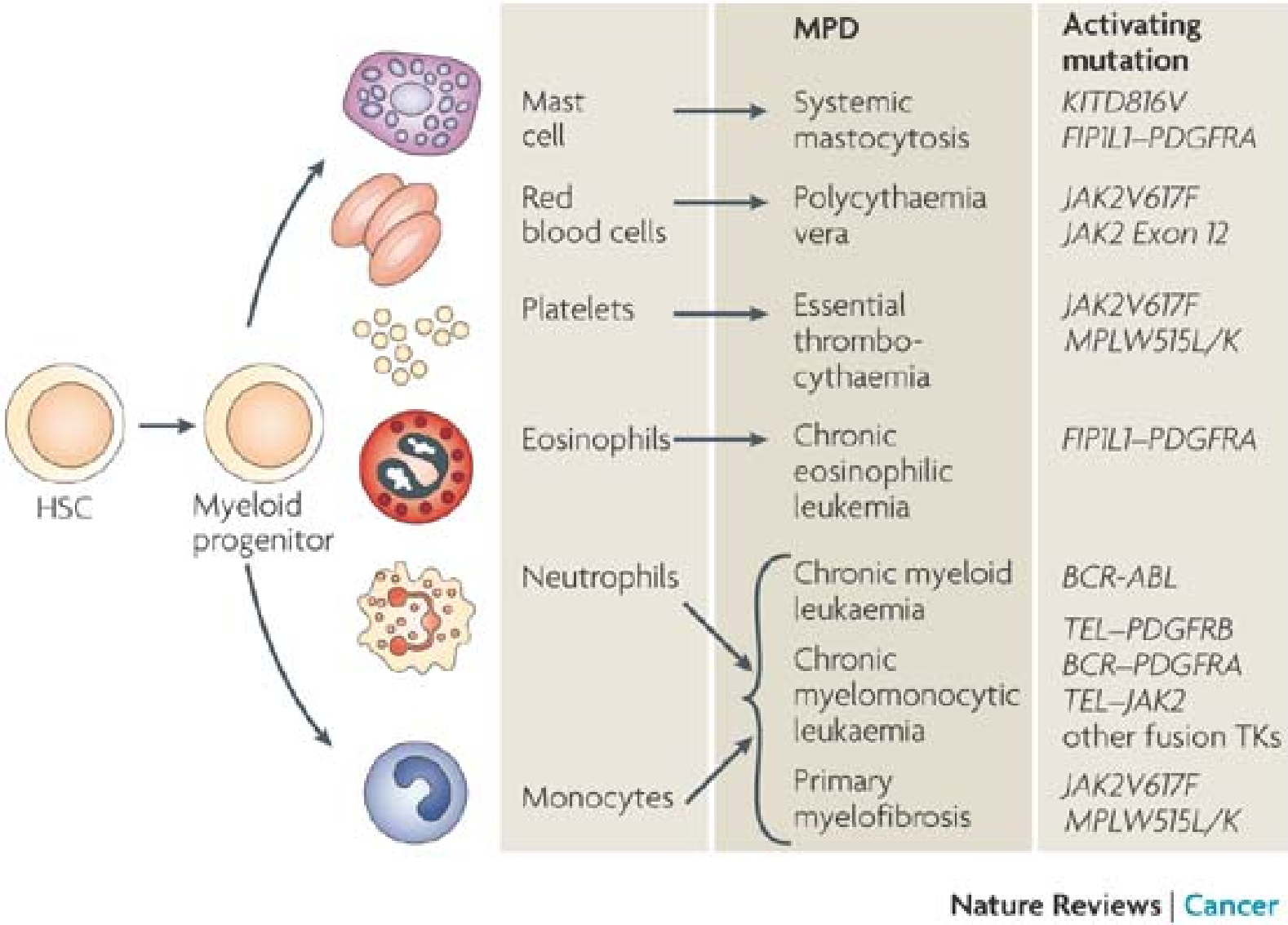
Erythropoietin receptor signaling.



Leukemia (2009) 23, 834–844;



¿¿¿ Y EN LA PATOLOGÍA ???



Classification and molecular pathogenesis of the MPD

Nature Reviews Cancer 7, 673-683 (September 2007)

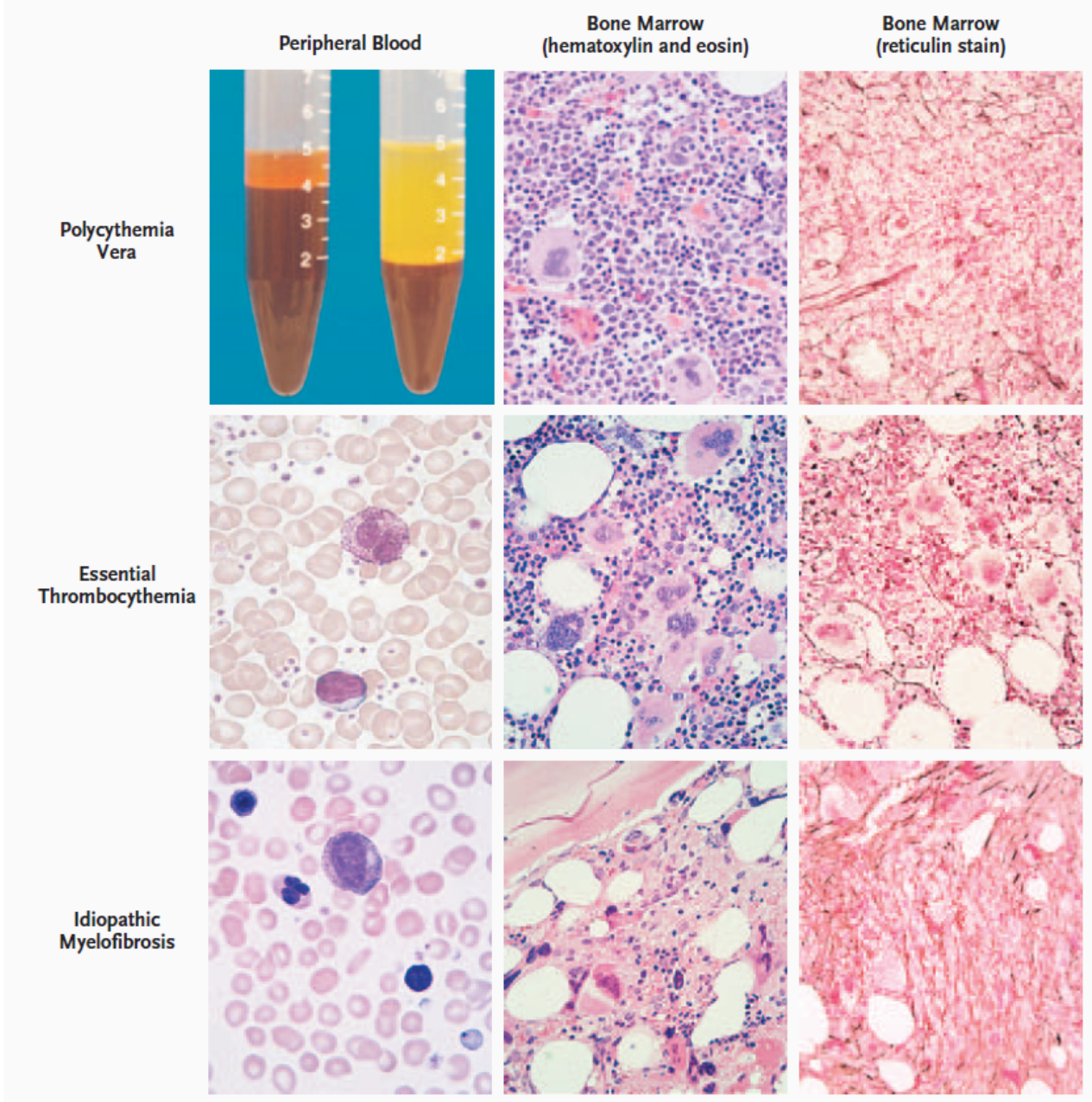
Table 2. Molecular Lesions Associated with the Myeloproliferative Disorders.*

Abnormality	Association
Recurrent genetic lesions	
BCR-ABL	Chronic myeloid leukemia (100%)[1]
JAK2 V617F	Polycythemia vera (95%),[6,26] essential thrombocythemia (50–60%),[27,28] idiopathic myelofibrosis (50–60%),[29,30] and other myeloid disorders (1–5%)[31-34]
MPL W515K/L	Idiopathic myelofibrosis (5%) and essential thrombocythemia (1%)[35,36]
KIT mutations	Systemic mastocytosis[15,37]
FIP1L1–PDGFRA	Chronic eosinophilic leukemia[18,38]
PDGFRB fusion genes	Chronic myelomonocytic leukemia (rare)[16]
FGFR fusion genes	Chronic myelomonocytic leukemia (rare)[17]
Other cytogenetic lesions	
Trisomy 9	Amplifies *JAK2* gene and associated with *JAK2* V617F mutation[39]
Trisomy 8	Found in myeloproliferative disorders, myelodysplasia, and acute myeloid leukemias; target genes not identified
Trisomy 1q	Caused by duplication, trisomy, or unbalanced translocations[40]
20q deletion	Found in myeloproliferative disorders and myelodysplasia[41]; associated with JAK2 V617F mutation[39] and precedes it in some cases[42]; target genes not identified[41]
5q and 7q deletions	Thought to reflect changes secondary to cytotoxic therapy[40]; target genes not identified
13q deletion	Associated with idiopathic myelofibrosis; overlap of commonly deleted region and the region for chronic lymphocytic leukemia[40]
Dysregulated genes and proteins	
BCL-XL	Overexpressed in polycythemia vera[43] as a result of constitutive JAK–STAT signaling; antiapoptotic effects in erythroid cells[44,45]
NFE2	Up-regulated in *JAK2*-positive myeloproliferative diseases[46,47]; may affect erythroid differentiation[48,49]
PRV1	RNA levels increased in polycythemia vera[50,51] but unlikely to play a direct role in disease pathogenesis since protein levels are not increased[51]
MPL	Surface levels of protein decreased and aberrantly glycosylated in myeloproliferative disorders[52,53]; role in disease pathogenesis unclear

* FIP1L1 denotes FH interacting protein 1–like 1, *PDGFRA* platelet-derived growth-factor receptor alpha polypeptide, *PDGFRB* platelet-derived growth-factor receptor beta polypeptide, *FGFR* fibroblast growth-factor receptor, *BCL-XL* B-cell leukemia/lymphoma 2–like protein X long-transcript variant, *NFE2* nuclear factor erythroid–derived 2, *PRV1* polycythemia rubra vera 1, and MPL thrombopoietin receptor.

N Engl J Med 2006;355:2452-66.

Características habituales de las MPN en la morfología



N Engl J Med 2006;355:2452-66.

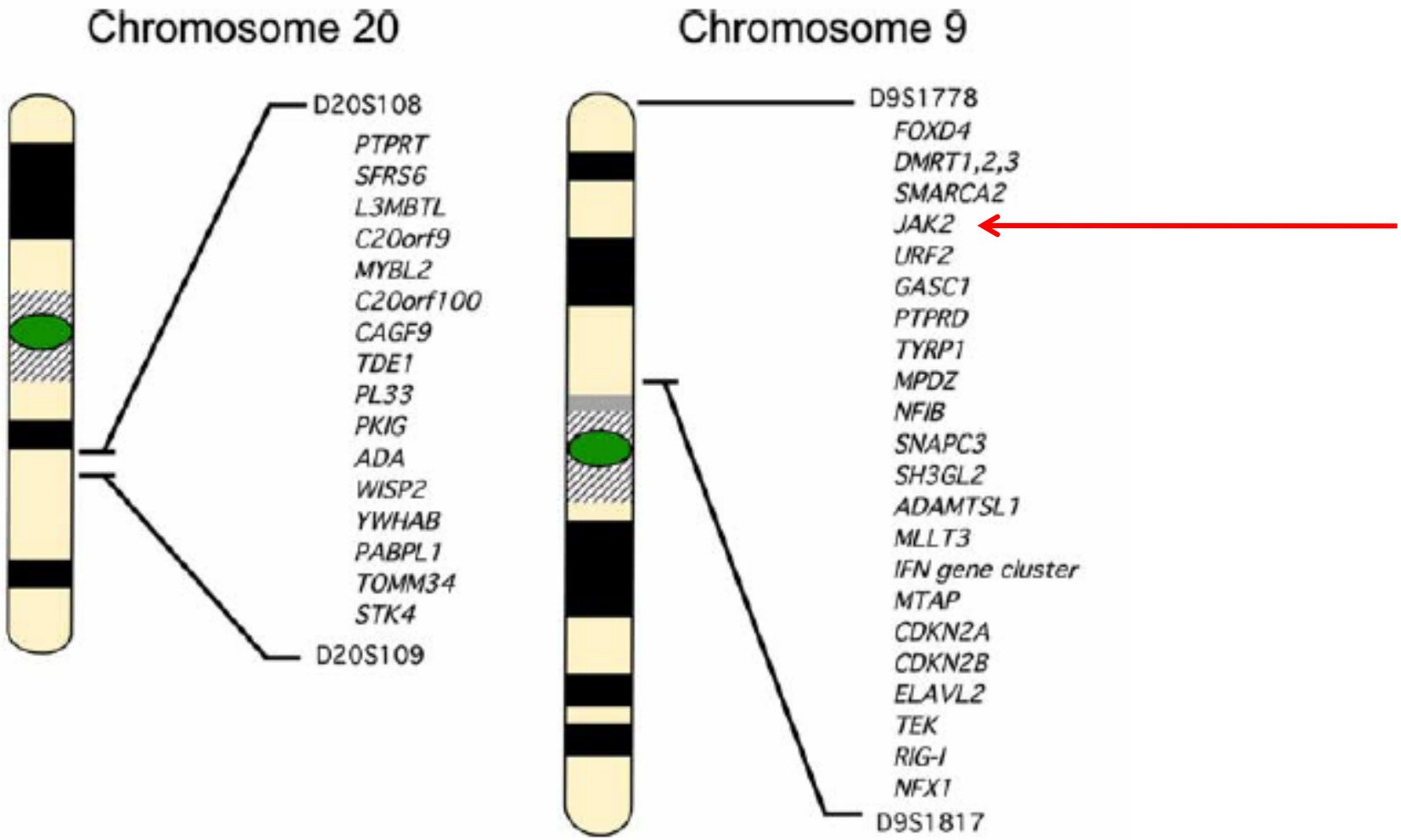
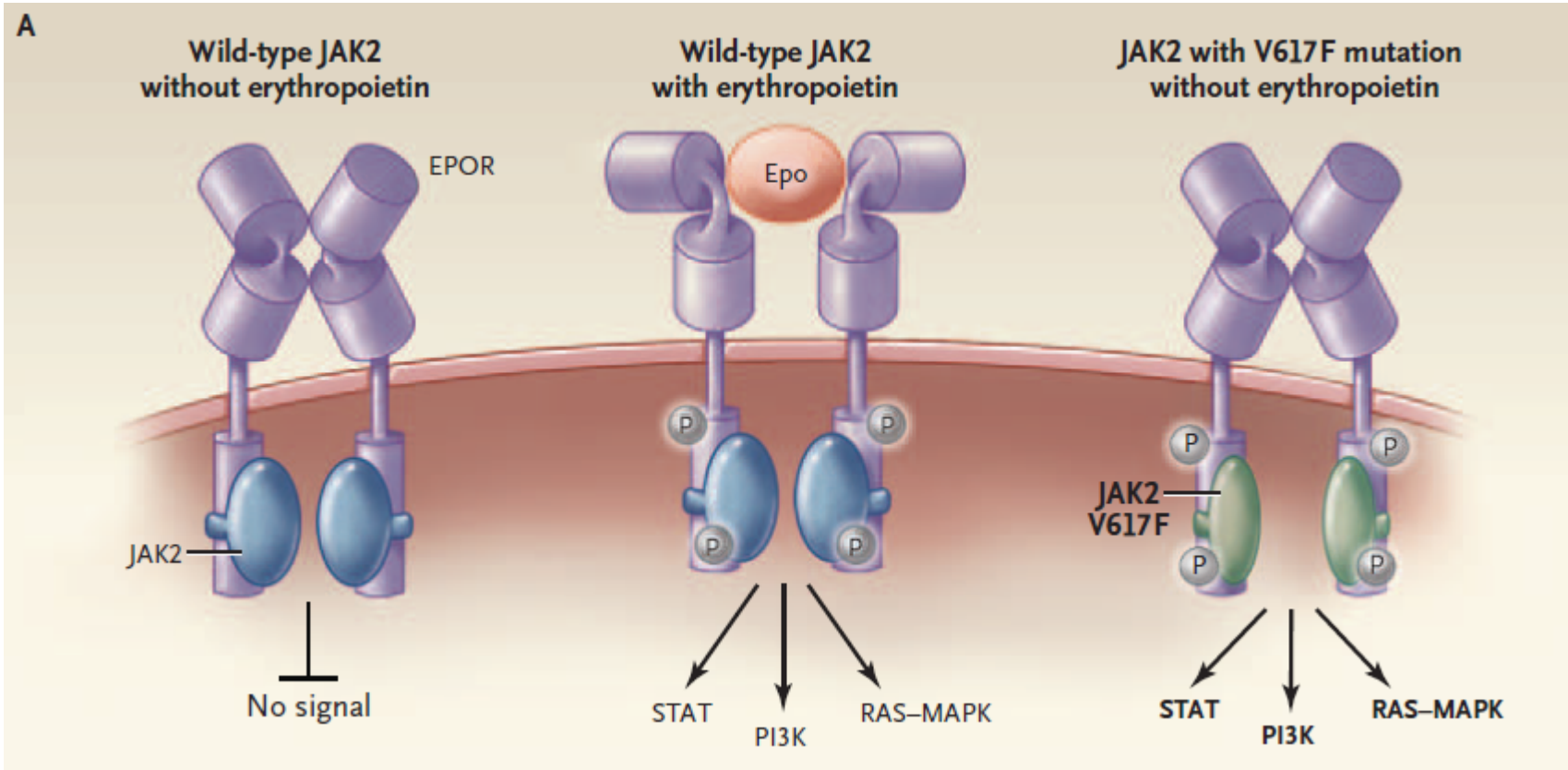
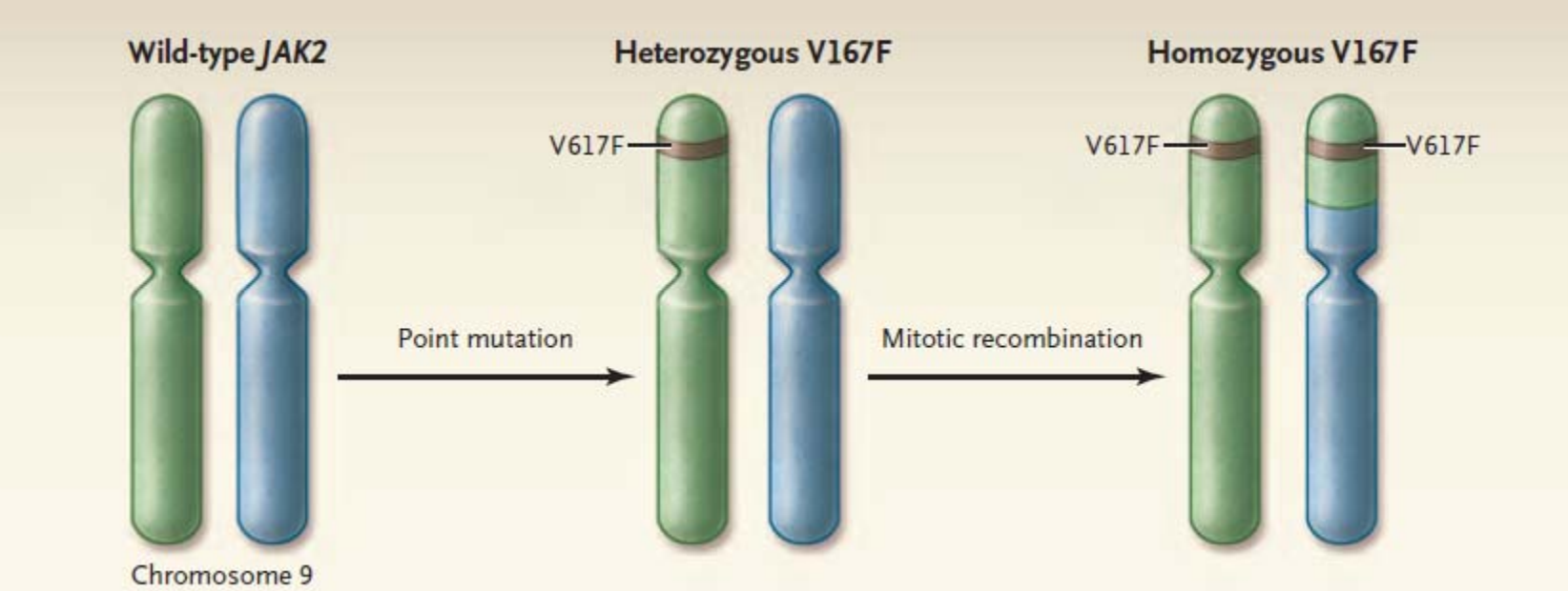


Figure 1 List of candidate genes within the minimal deleted region on chromosome 20q and the minimal loss of heterozygosity region on chromosome 9p.



La activación de JAK2 “wild type” vs JAK2 V617F, que aumenta la sensibilidad al ligando (eritropoietina) y genera el fenotipo de la Policitemia rubra vera.

N Engl J Med 2006;355:2452-66.



La ubicación de JAK2 “wild type” en el brazo corto del cromosoma 9, que permitió su identificación en pacientes con amplificación anormal de este segmento (9p) y MPN.

La mutación JAK2 V617F puede ser heterozigota u homozigota, en la Trombocitemia esencial lo habitual es la heterozigocidad, mientras que en Policitemia rubra vera hasta un cuarto de los pacientes es homozigoto. Los Homozigotos cursan cuadros clínicamente más sintomáticos.

N Engl J Med 2006;355:2452-66.

Acquired mutation of the tyrosine kinase JAK2 in human myeloproliferative disorders

E Joanna Baxter, Linda M Scott*, Peter J Campbell*, Clare East, Nasios Fourouclas, Soheila Swanton, George S Vassiliou, Anthony J Bench, Elaine M Boyd, Natasha Curtin, Mike A Scott, Wendy N Erber, the Cancer Genome Project†, Anthony R Green*

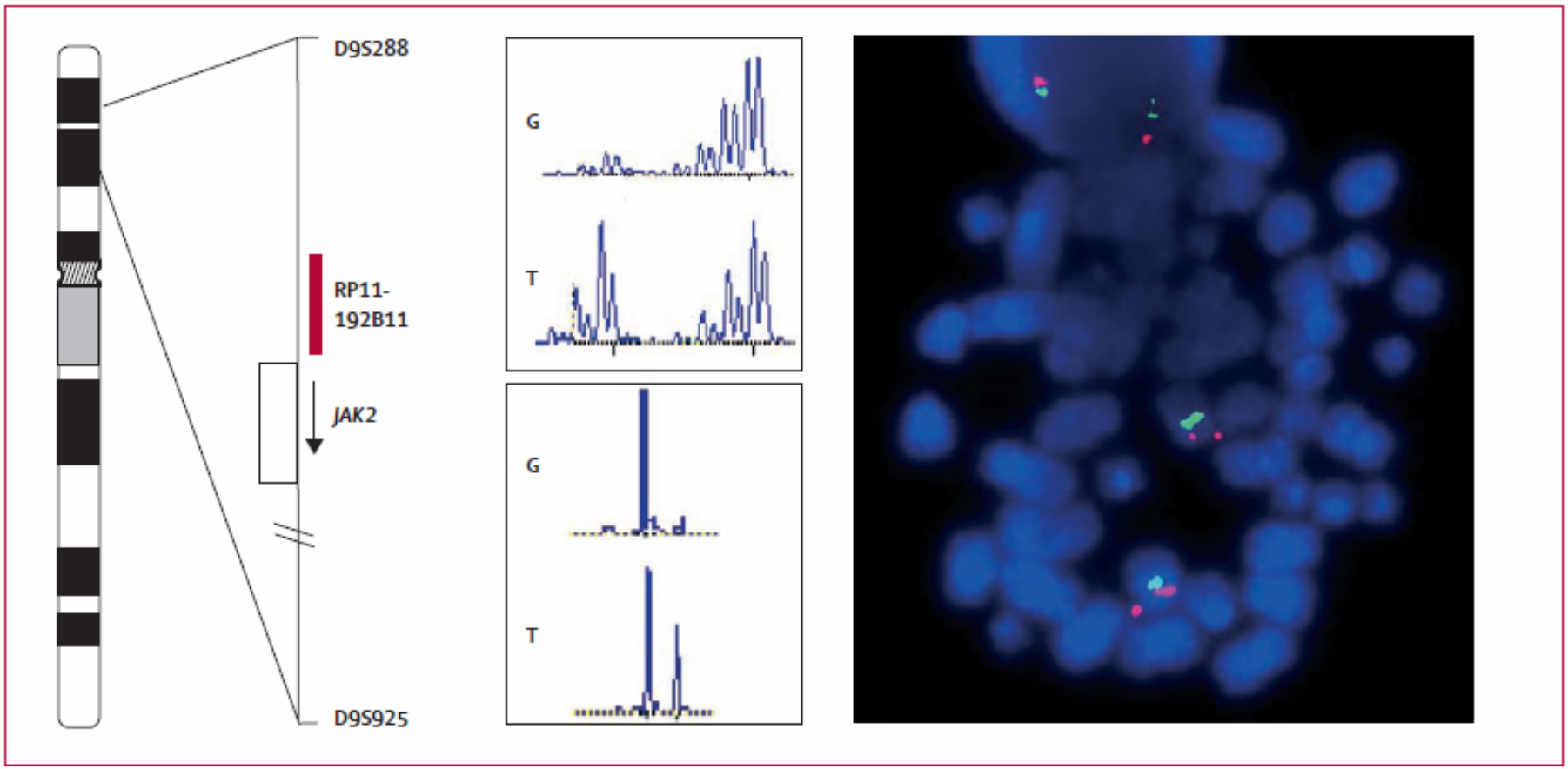


Figure 4: **Diagrammatic representation of chromosome 9 showing the markers used for microsatellite PCR analysis and FISH**
The middle two panels show microsatellite PCR results, showing loss of heterozygosity for D9S288 (upper) and D9S925 (lower) in a patient with polycythaemia vera. The panel on the right shows FISH analysis on the same patient, showing signals for BAC RP11-192B11 on both chromosome 9 homologs. Green=chromosome 9 centromeric probe. Red=BAC RP11-192B11.

Lancet 2005; 365: 1054–61

	Wild-type	Val617Phe
Essential thrombocythaemia		
Number of patients	22	29
Age (years)	54 (17)	55 (16)
Female	12 (55%)	15 (52%)
Haemoglobin (g/L)	141 (13)	141 (12)
White-cell count ($\times 10^9$/L)	9·4 (2·7)	10·9 (4·1)
Platelet count ($\times 10^9$/L)	926 (242)	1024 (346)
Spleen palpable	5 (23%)	2 (7%)
Abnormal karyotype	4 (18%)	3 (10%)
Complications		
Thrombosis	4	8
Transformation to myelofibrosis	1	1
Transformation to polycythaemia vera	0	2
Idiopathic myelofibrosis		
Number of patients	8	8
Age (years)	60 (9)	65 (8)
Female	5 (63%)	1 (13%)
Haemoglobin (g/L)	102 (28)	107 (26)
White-cell count ($\times 10^9$/L)	13·1 (8·9)	21·6 (12·3)
Platelet count ($\times 10^9$/L)	509 (258)	364 (194)
Spleen size (cm below costal margin by palpation)	7·4 (4·0)	6·4 (6·9)
Abnormal karyotype	0	2 (25%)
Complications		
Thrombosis	1	1
Major haemorrhage	0	2
Death	1	1

Data are mean (SD) or number of patients (%). No significant differences noted between patients with and without the mutation.

Table 3: **Clinical characteristics at diagnosis of patients with and without the JAK2 mutation**

Lancet 2005; 365: 1054–61C

Frecuencias de la Mutación V617F de JAK2 en las MPN

Disease	Frequency
Polycythaemia vera	81–99%
Essential thombocytosis	41–72%
Primary myelofibrosis	39–57%
Chronic myelomonocytic leukaemia	3–9%
Myelodysplasia*	3–5%
Acute myeloid leukaemia‡	<5%

Table 1 The frequency of JAK2 V617 mutation in hematopoietic disorders

Diagnosis	Frequency of JAF2 V617F (%)	Frequency of homozygosity (%)
MPN		
PV	>90	24-27
ET	≈50	3-4
CIMF	≥50	6-18
CML	Rare	ND
aCML	<20	ND
HES	<2	
Systemic mastocytosis	Rare	ND
MPN/MDS		
CMML	<5	ND
JMML	<20	ND
MDS	≈5	ND
AML		
De novo AML	1	ND
AML arising from JAK2+ MPN	≤50	ND
ALL	None	ND
Hodgkin lymphoma	None	ND
Mediastinal B-cell lymphoma	None	ND

Abbreviation: ND, not done.

Human Pathology (2008) **39**, 795–810

JAK2 V617F y las MPN

- Es muy frecuente en policitemia rubra vera, confirmando el diagnóstico.
- En Trombocitosis esencial bordea el 50% de los pacientes, es parte del estudio diagnóstico y permite evitar el descarte de múltiples patologías reactivas.
- En Mielofibrosis Primaria es muy infrecuente, por lo que si bien apoya el diagnóstico (diferenciando de las reactivas) no es de mayor utilidad.

Rol de JAK2

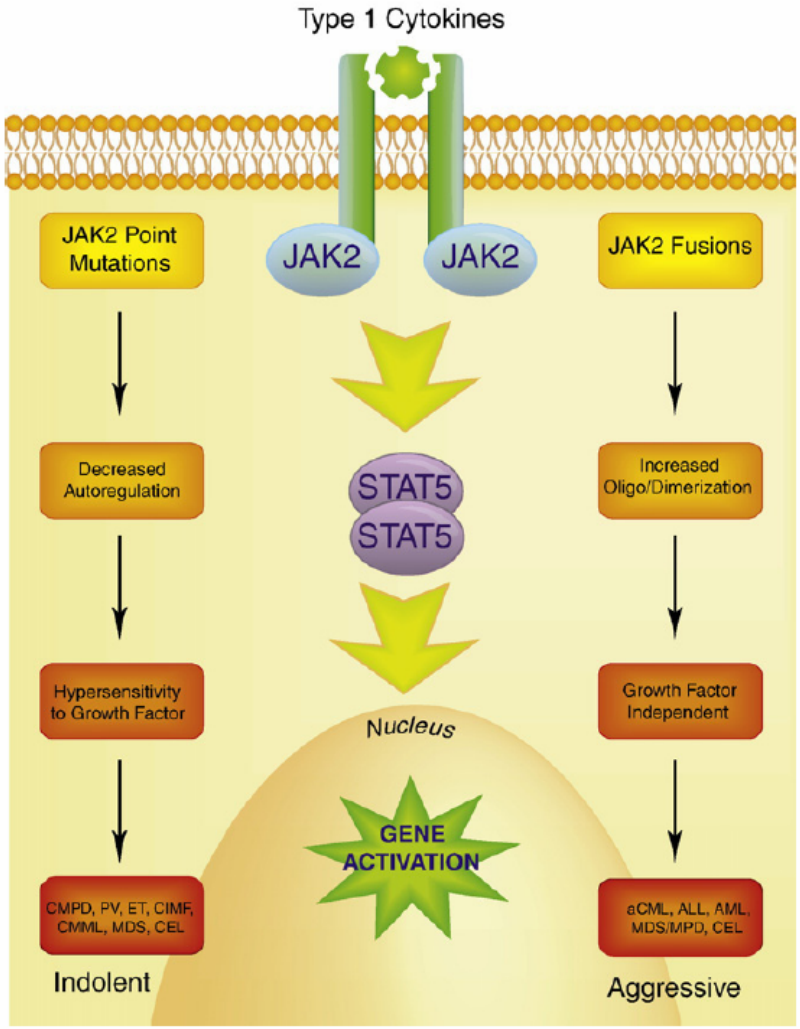


Fig. 4 Model of JAK2 mutations and translocations associated with hematopoietic disorders. JAK2 point mutations and deletions lead to hypersensitivity to growth factors through decreased autoregulation. JAK2 fusions may cause increased oligomerization and lead to growth factor–independent autoactivation of JAK2. Compared with JAK2 mutations, JAK2 fusions are likely associated with more aggressive diseases, such as AML, ALL, aCML, and myelofibrosis.

- En cuatro años se ha relacionado a JAK2 y sus diversas mutaciones con múltiples entidades neoplásicas, NO sólo con MPN.
- En las MPN las mutaciones tienen un rol incrementando la sensibilidad a los factores de crecimiento, pero no serían iniciadores del cambio neoplásico.

Human Pathology (2008) **39**, 795–810

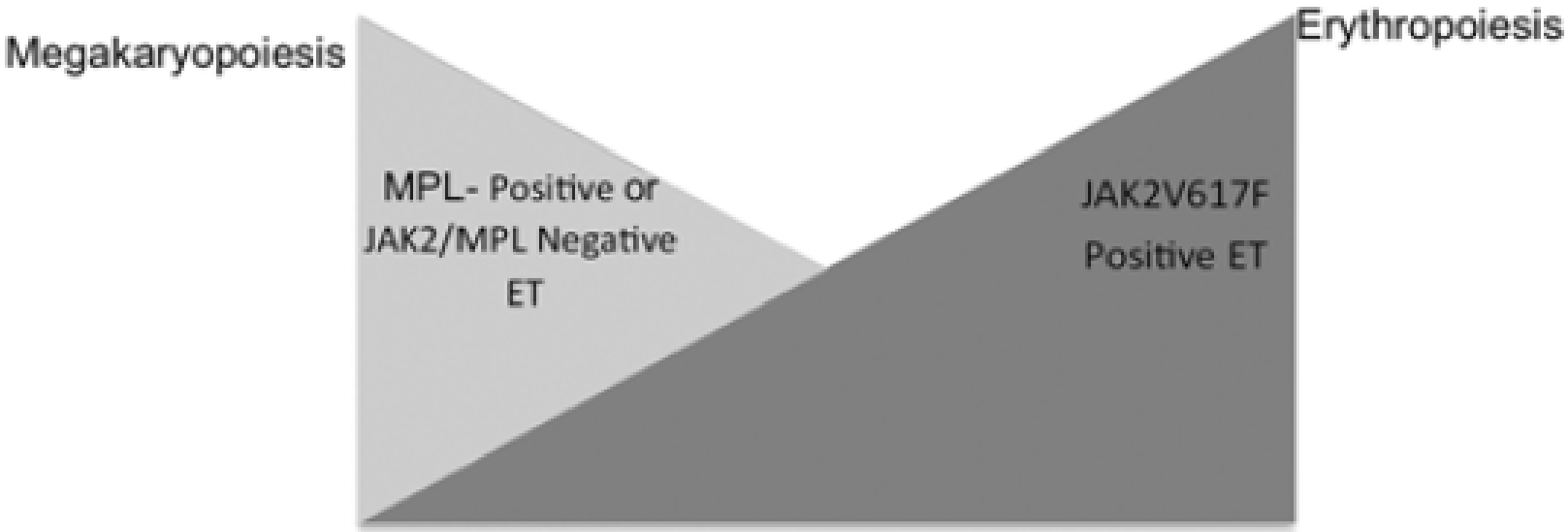
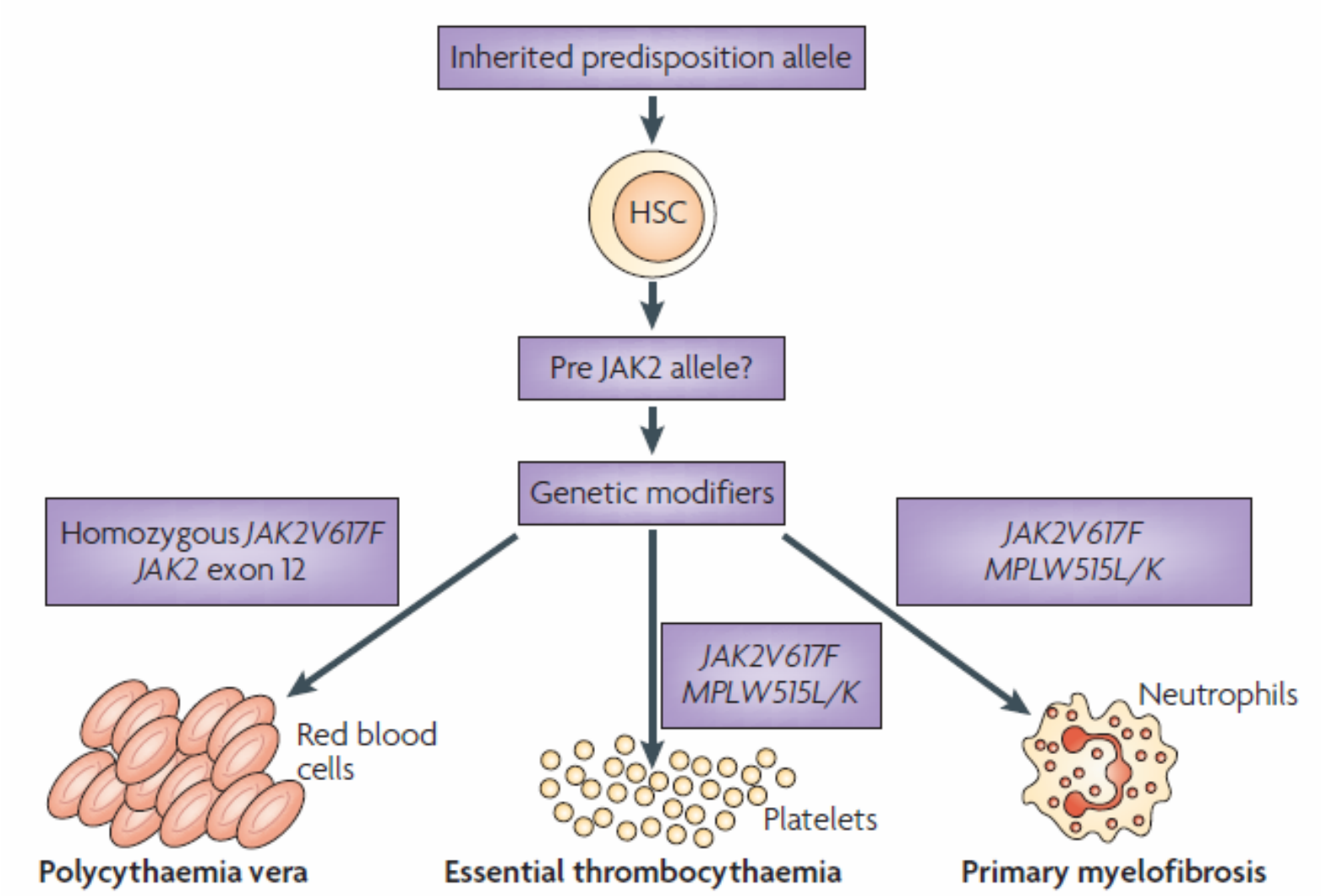


Figure 1. Model of relative erythropoiesis and megakaryopoiesis based on JAK2/MPL mutational status in essential thrombocythemia (ET). JAK2V617F positive ET is characterized by a relative increase in erythropoiesis, which manifests as a higher hemoglobin level and reduced erythropoietin level, whereas MPL-positive disease or MPL/JAK2-negative disease is associated with higher platelet counts and reduced hematocrit.

Hematology Levine and Heaney 2008 (1): 76.



Current model of the pathogenesis of PV, ET and PMF

Nature Reviews Cancer 7, 673-683 (September 2007)

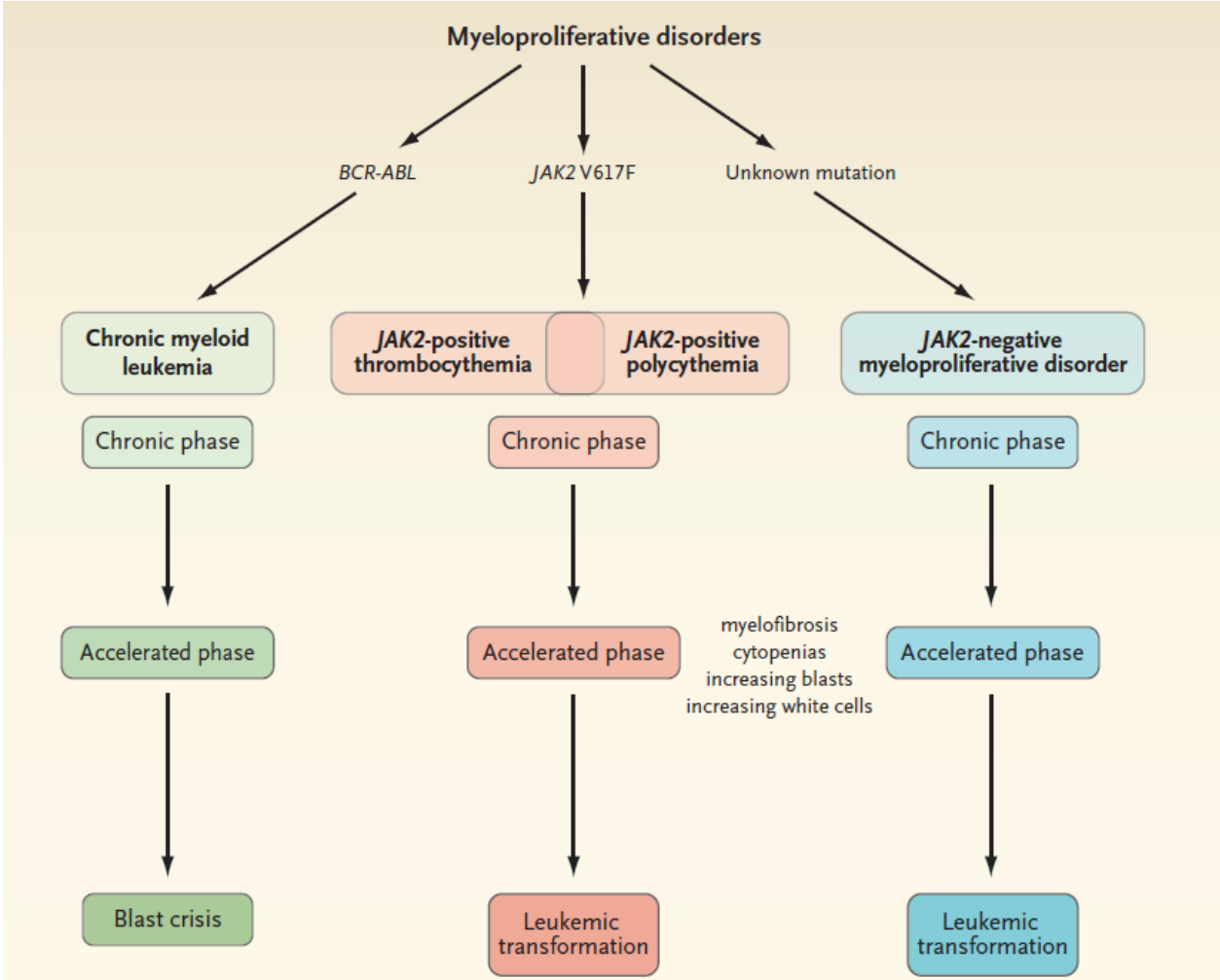
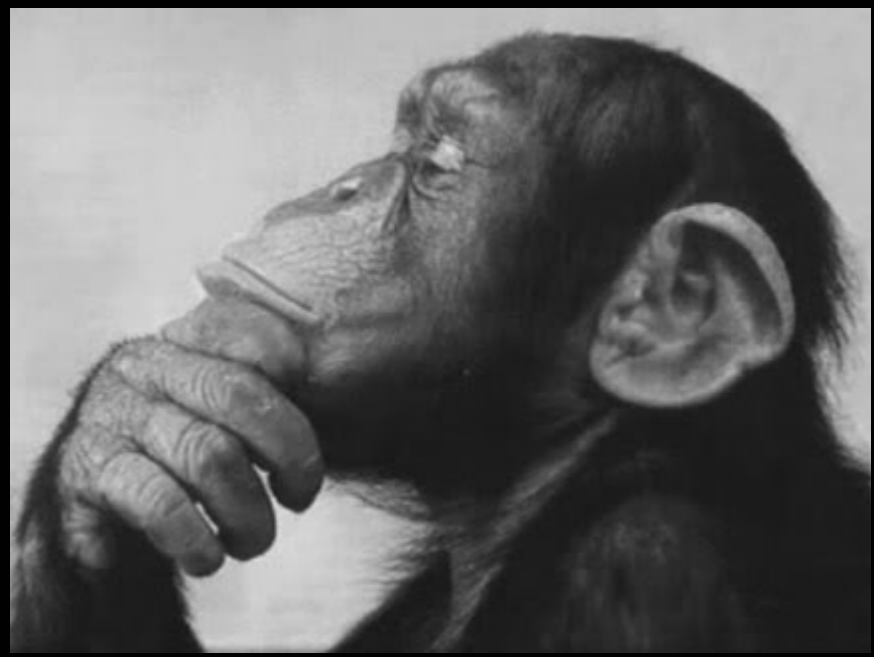


Figure 3. Classification of the Myeloproliferative Disorders on the Basis of Molecular Pathogenetic Characteristics.

Chronic myeloid leukemia is defined by the *BCR-ABL* fusion gene and characterized by three stages of disease progression, from the chronic phase through the accelerated phase to blast crisis. Analogously, *JAK2*-positive thrombocythemia and polycythemia have overlapping phenotypes in the chronic phase and can progress to an accelerated phase, which is manifested as myelofibrosis or other complications. Leukemic transformation can also occur. *JAK2*-negative disease follows similar patterns of progression. The disorder that is currently called idiopathic myelofibrosis or agnogenic myeloid metaplasia is clinically indistinguishable from the myelofibrotic transformation of polycythemia vera or essential thrombocythemia. Therefore, this disorder may be an accelerated phase of polycythemia vera or thrombocythemia. Many patients with polycythemia vera who do not have the V617F mutation have other *JAK2* mutations, and therefore truly *JAK2*-negative polycythemia vera is probably extremely rare.

N Engl J Med 2006;355:2452-66.



Work Up

Morfología

- Sigue siendo la primera manera de enfrentar la enfermedad, aunque frecuentemente es poco específica y presenta sobreposiciones entre diferentes patologías (trombocitosis esencial y mielofibrosis inicial, por ejemplo).
- Requiere Hemopatólogos entrenados y tiene a la fecha un valor más bien pronóstico que predictivo.
- Dado lo anterior la OMS se basa cada vez más en parámetros cuantitativos.

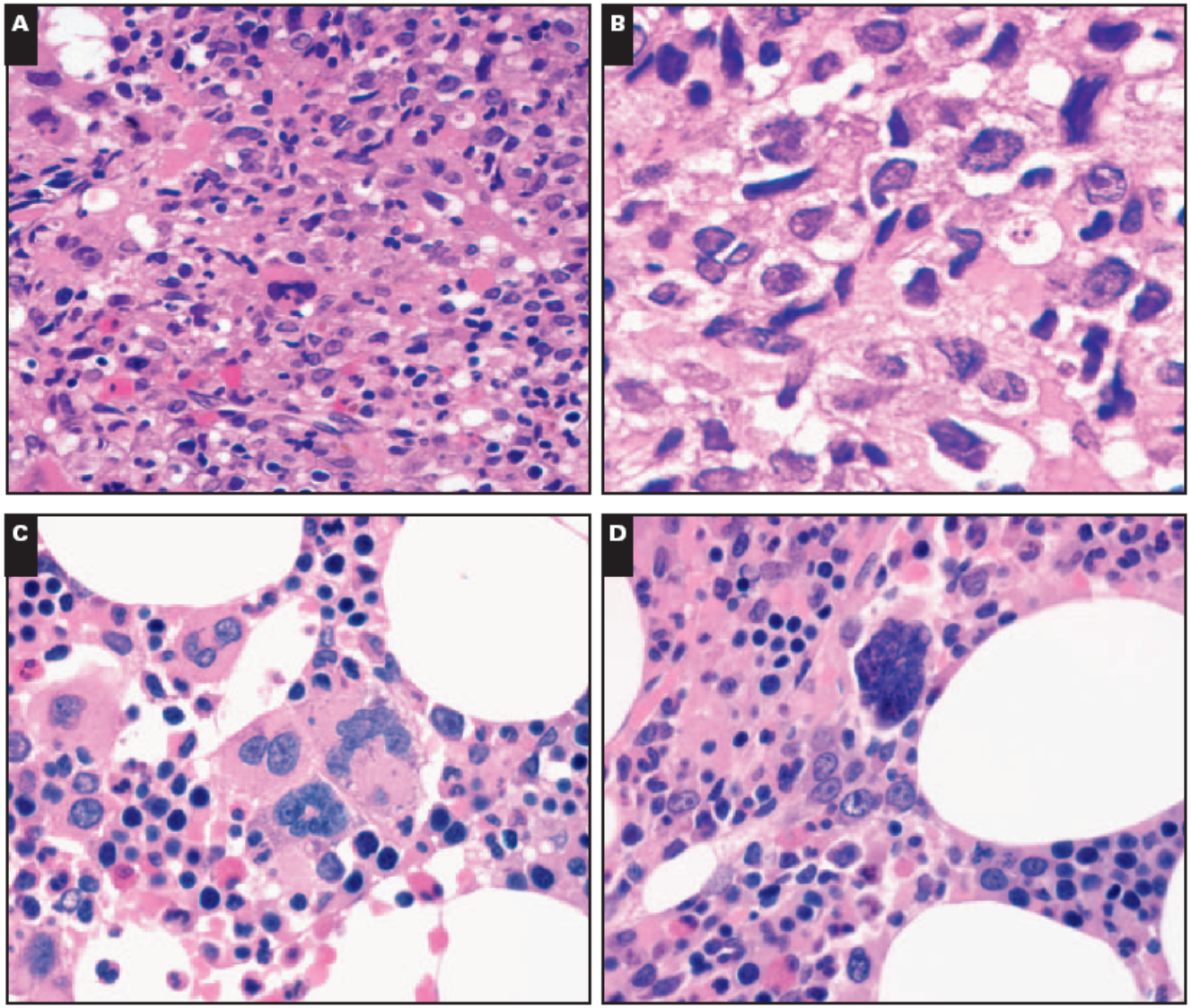
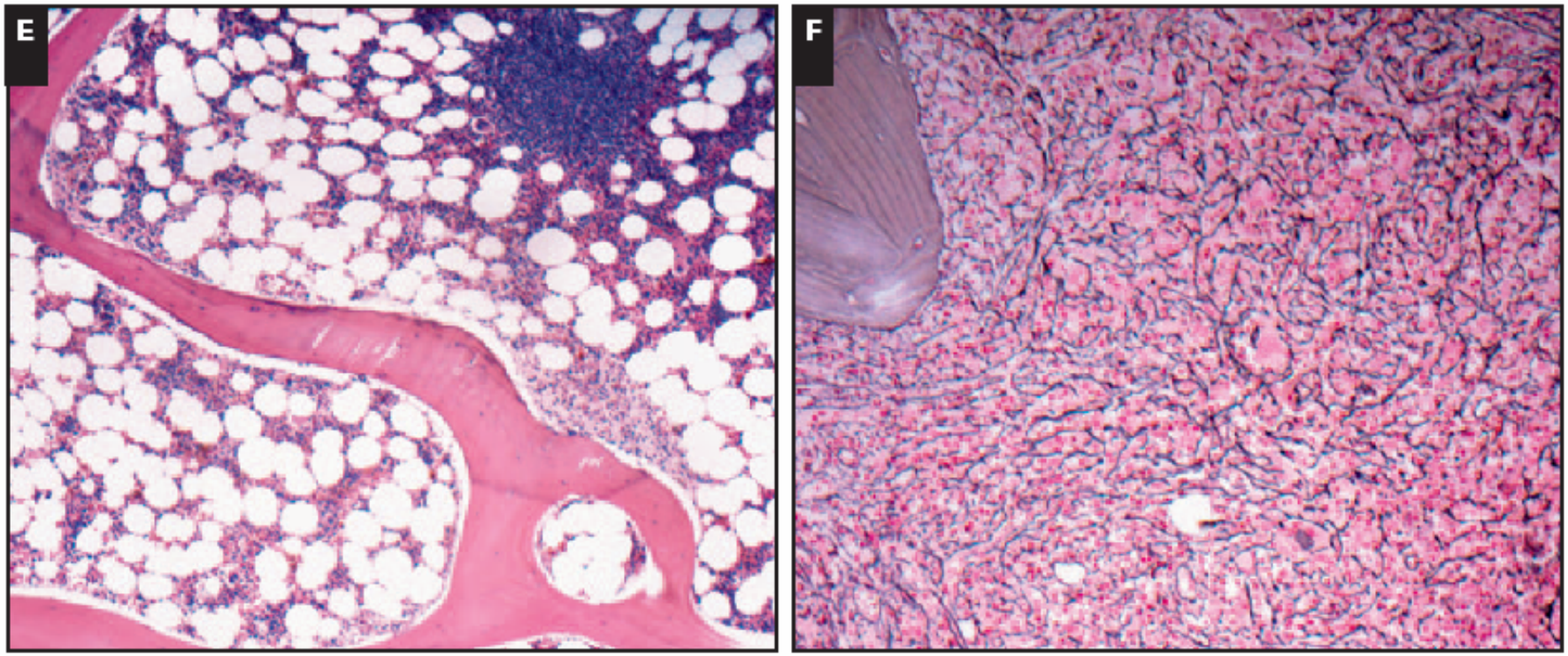


Image 4 Polycythemia vera and myelofibrosis (**A** and **B**, Case 219; **C** and **D**, Case 110; **E** and **F**, Case 148). **A**, Chronic myeloproliferative neoplasm with hypercellular bone marrow showing loose clusters of megakaryocytes and left-shifted neutrophils (H&E). **B**, Patchy area with immature cells and blasts (H&E). **C**, Initial stage of primary myelofibrosis revealing a hypercellular bone marrow in the biopsy specimen with a dense small cluster of megakaryocytes and mild maturation defects (H&E). **D**, Large so-called naked nucleus of megakaryocyte in addition to slight increase in (mature) neutrophils (H&E). Contributed by C. Hanson and colleagues.



E, Autoimmune (reactive) myelofibrosis with hypocellular bone marrow biopsy specimen revealing an expansion of adipose tissue and prominent lymphoid aggregate (H&E). **F**, Marked reticulin fibrosis in follow-up bone marrow trephine biopsy specimen (reticulin stain). Contributed by R. Hasserjian.

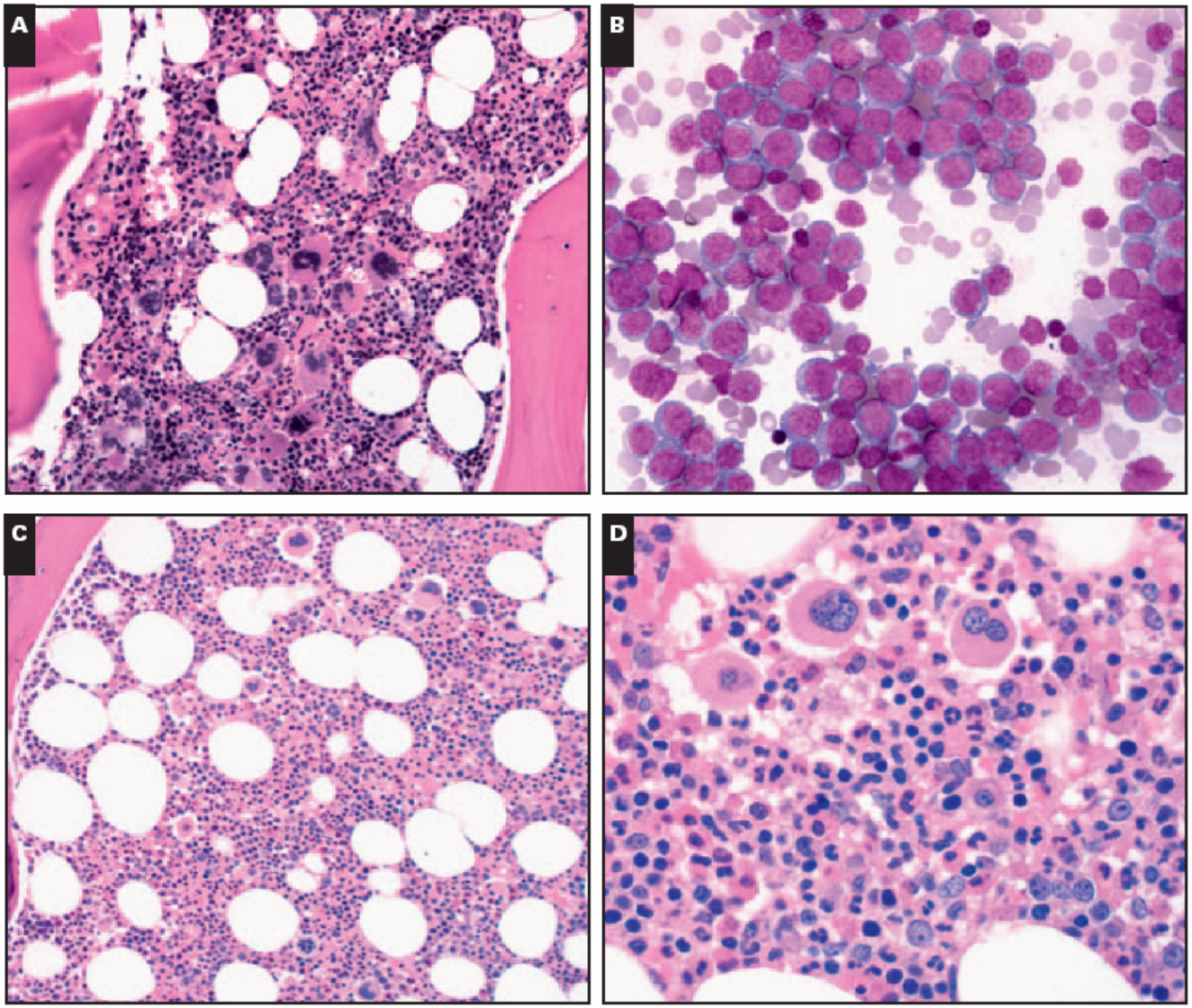


Image 5 Essential thrombocythemia vs early-stage primary myelofibrosis and reactive thrombocytosis (**A** and **B**, Case 94; **C** and **D**, Case 175). **A**, Initial primary myelofibrosis (first biopsy in 1999) with hypercellular bone marrow biopsy specimen showing a loose cluster of abnormal megakaryocytes and moderate granulocytic proliferation (H&E). **B**, Acute myeloid leukemia including posttherapy relapse (in 2005) with a prevalence of blasts in the bone marrow aspirate smear (Wright). Contributed by G. Wertheim and colleagues. **C**, Reactive thrombocytosis with hypercellular bone marrow biopsy specimen including erythropoiesis and mature neutrophils (H&E). **D**, Medium-sized to small megakaryocytes without clustering or maturation defects (H&E). Contributed by R. McClure.

Mild reticulin fibrosis in the bone marrow specimen (reticulin stain).

Am J Clin Pathol 2009;132:261-280

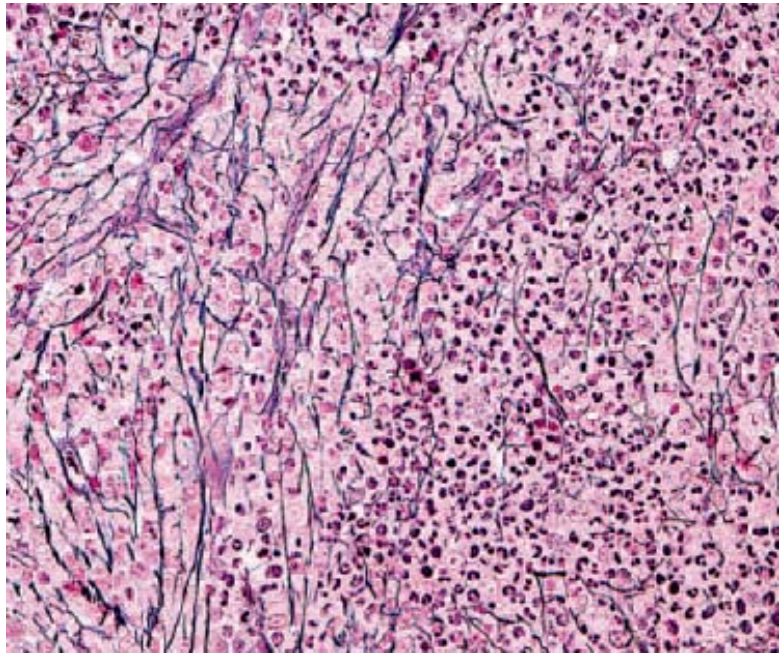


Table 2

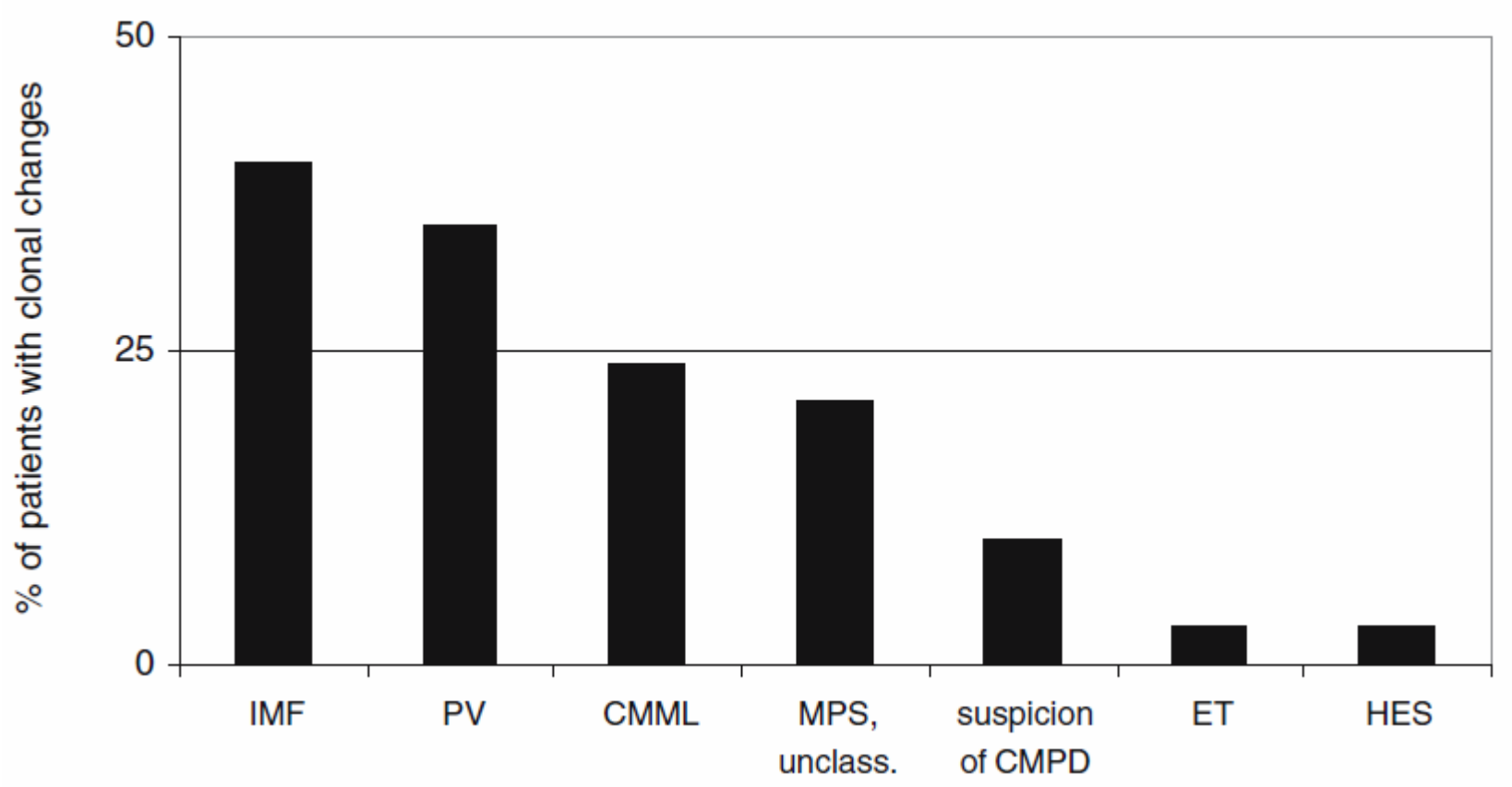
Relative Incidence (%) of Borderline to Marked Reticulin and/or Collagen Myelofibrosis[78] in Initially Performed Bone Marrow Biopsies Derived From About 1,300 Specimens With Philadelphia Chromosome–Negative Chronic Myeloproliferative Neoplasms Diagnosed According to the World Health Organization Classification[1,7]

	Grade of Myelofibrosis			
	0	1	2	3
Polycythemia vera	84	15	1	0
Primary myelofibrosis	27	38	17	18
Essential thrombocythemia	99	1	0	0

Citogenética

- Retiene notoria utilidad en el estudio de las MPN JAK2 V617F negativas, en especial para diferenciarlas de otras entidades y establecer clonalidad.

Citogenética



Ann Hematol (2005) 84: 250–257

Citogenética

Chromosomal change	Number of cases (n=409)	Percentage of all cases in CMPD	Percentage of all cases with cytogenetic abnormalities (n=90)	Number of reported cases according to Mitelman database 2004 (*)
+8	14	3.4%	15.6%	100
+9	9	2.2%	10%	78
del(20q)	8	2.0%	8.9%	166
Gain of 1q	7	1.7%	7.8%	25
+19	6	1.5%	6.7%	12
−7	6	1.5%	6.7%	85
del(13q)	6	1.5%	6.7%	72
−Y	6	1.5%	6.7%	34
+21	4	1.0%	4.4%	36
i(17q)	4	1.0%	4.4%	17
del(12p)	3	0.7%	3.3%	5

Table 3 Frequency of the recurrent abnormalities in patients with CMPD (n=409)

Ann Hematol (2005) 84: 250–257

Citogenética

Chromosomal change	PV (n=43)	ET (n=31)	IMF (n=52)	HES (n=29)	MPS, unclassifiable (n=157)	CMML (n=97)
−Y	–	–	–	1 (3%)	2 (1%)	3 (3%)
−7	–	–	–	–	1 (0.6%)	5 (5%)
+8	2 (5%)	–	2 (4%)	–	4 (6%)	4 (4%)
+9	3 (7%)	–	3 (6%)	–	3 (2%)	–
+19	–	–	1 (2%)	–	2 (1%)	3 (3%)
+21	–	–	–	–	2 (1%)	2 (2%)
Gain of 1q	1 (2%)	–	3 (6%)	–	3 (2%)	–
del(12p)	1 (2%)	–	–	–	1 (0.6%)	1 (1%)
del(13q)	1 (2%)	–	5 (10%)	–	–	–
del(20q)	1 (2%)	–	4 (8%)	–	3 (2%)	–
i(17q)	–	–	–	–	2 (1%)	2 (2%)

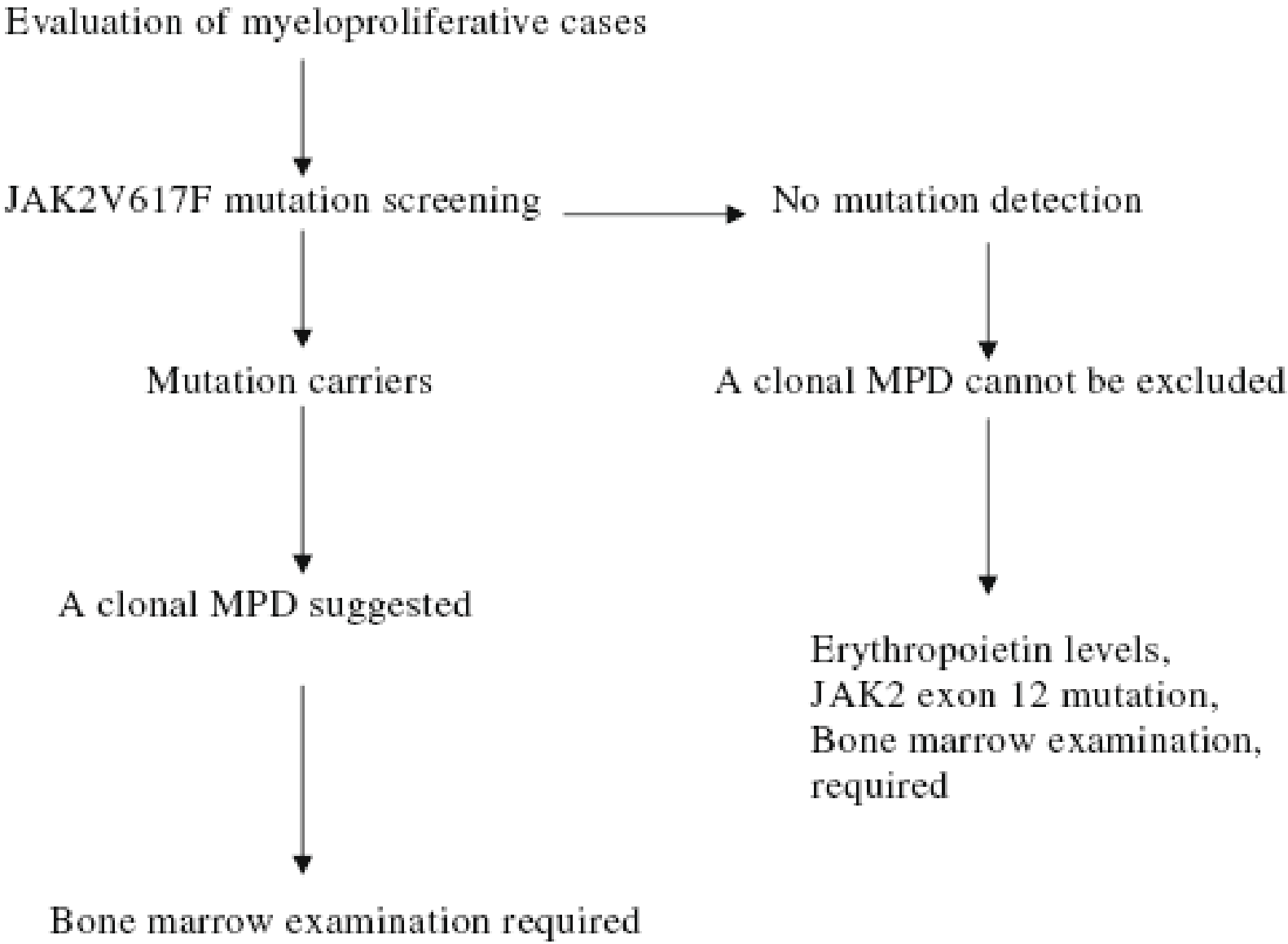
Table 4 Frequency of specific recurrent chromosomal changes in the different cohorts

Ann Hematol (2005) 84: 250–257

Estudio de JAK2

- Opciones de determinación Molecular :
  - Secuenciación.
  - PCR Alelo - específica.
  - Real Time PCR cuantitativa y análisis de la curva de hibridación del DNA.
  - Pirosecuenciación.
- Es importante investigar la existencia de otras mutaciones (exon 12, por ejemplo), dado lo cual es importante secuenciar a los pacientes negativos a la hibridación .

Human Pathology (2008) **39**, 795–810



A.D. Panani / Cancer Letters 284 (2009) 7–14

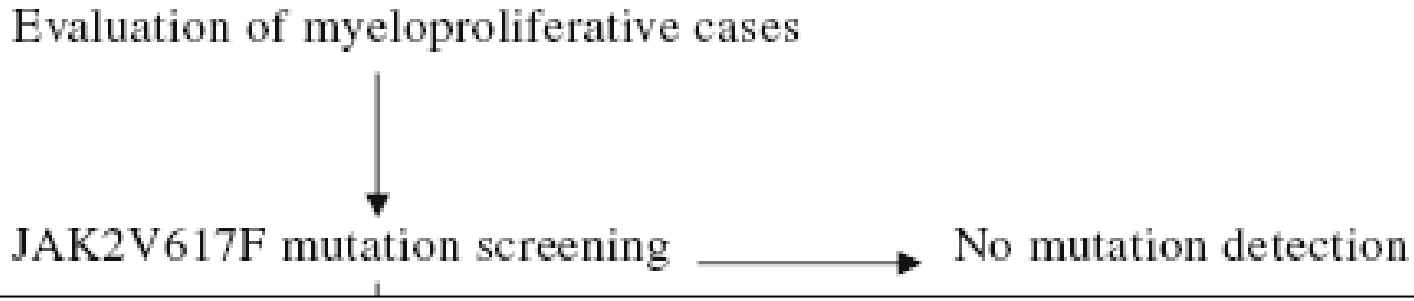
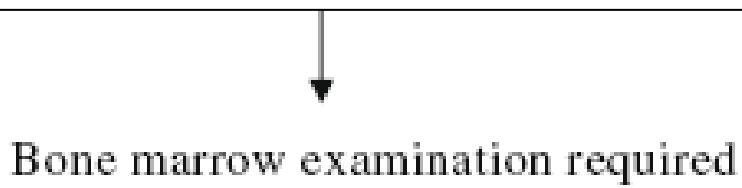
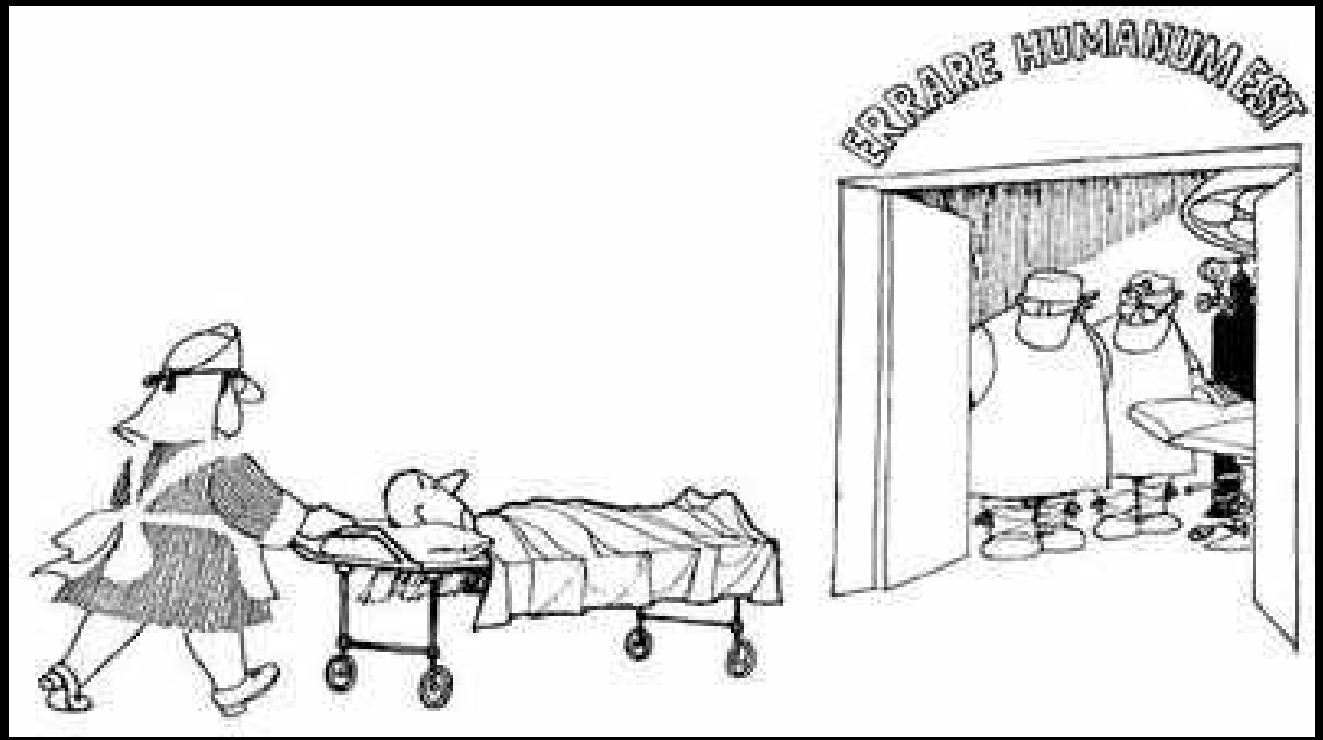


Table 1
Indications for JAK2 mutation screening in clinical practice.

1. Increased hemoglobin level
2. Thrombocytosis
3. Granulocytosis
4. Splenomegaly of unknown origin
5. Abdominal vein thrombosis





Tratamiento ?

-: Tratamiento Actual :-

- Tratamiento esencialmente sintomático que busca prevenir complicaciones trombóticas y dar soporte.
- En Mielofibrosis el transplante tiene un rol en menores de 50 años.

			Myelofibrosis	
Risk categories	**Essential thrombocythaemia (ET)**	**Polycythaemia vera (PV)**	**Age < 50 years**	**Age ≥ 50 years**
Low	Low-dose aspirin	Low-dose aspirin + phlebotomy	Observation or experimental drug therapy	Observation or experimental drug therapy
Intermediate	Low-dose aspirin*	Low-dose aspirin* + phlebotomy	Experimental drug therapy or RIC transplant	Experimental drug therapy or conventional therapy
High	Low-dose aspirin + hydroxyurea	Low-dose aspirin + phlebotomy + hydroxyurea	Experimental drug therapy or full transplant	Experimental drug therapy or RIC transplant

*Clinically significant acquired von Willebrand disease should be excluded before the use of aspirin in patients with a platelet count over 1000×10^9 per L. Risk stratification of ET and PV according to thrombotic risk[114]. High risk: age ≥ 60 years or previous thrombosis; intermediate-risk: age < 60 years and no previous thrombosis, but with either platelet count > 1500×10^9 per L or cardiovascular risk factors (tobacco use, diabetes mellitus, hypertension and/or hyperlipidaemia). Risk stratification of primary myelofibrosis (Mayo Prognostic Scoring System[115]): one point each for haemoglobin < 10 g per dL, white blood cell count < 4 or > 30×10^9 per L, platelet count < 100×10^9 per L, or monocyte count > 1×10^9 per L. Low-risk score = 0; intermediate-risk score = 1; high-risk score ≥ 2. RIC, reduced-intensity conditioning.

Drug	Company	Phase	Indication	Route	Primary target
JAK2 inhibitors					
INCB01842447	Incyte	Phase I/II	Myelofibrosis	Oral	JAK2
XLO1945	Elelixis	Phase I	Myelofibrosis	Oral	JAK2
TG10134841	TargeGen	Phase I/II	Myelofibrosis	PMF	JAK2
HDAC inhibitor					
ITF235767	Italfarmaco	Phase II	Essential thrombocythemia, Polycythemia vera, Myelofibrosis	Oral	HDAC
Methyltransferase inhibitor					
5-azacitidine[58]	Pharmion	Phase II	Myelofibrosis	Subcute	DNA methyltransferase
Drugs targeting angiogenesis					
CC-4047 (Actimid®)	Celgene Corp.	Phase I/II	Myelofibrosis	Oral	angiogenesis
Bevacizumab (Avastin®)	Genentech	Phase II	Myelofibrosis	I.V.	VEGF
Sunitinib	Pfizer	Phase II	Myelofibrosis	Oral	PDGFR VEGFr, FLT-3, c-KIT
Others					
MK-0457 (VX680)	Merck	Phase I	Relapsed/refractory hemato-logical malignancies, including JAK2617V>F-positive MPD	I.V.	Aurora kinases (A,B,C)
CEP-70149	Cephalon	Phase II	Myelofibrosis	Oral	FTL3
AT9283	Astex Therapeutics	Phase I/II	Myelofibrosis	I.V.	Aurora kinases
GX15-070MS	Gemin X	Phase II	Myelofibrosis	I.V.	Bcl-2

Hematology, Jan 2008; 2008: 83 - 91.

Tratamientos a Futuro

- Existen al menos 5 grupos de trabajo, con estudios fundamentalmente a nivel de Fases I y II publicados y algunos Fase III en reclutamiento …

"Workshop on Philadelphia positive and Philadelphia negative myeloproliferative Disorders"
Sonoma, California – 11 y 12 de Diciembre 2008
Leukemia (2009), 1–8

Table 1 Currently reported efficacy for JAK2 inhibitors from clinical trials in patients with myelofibrosis

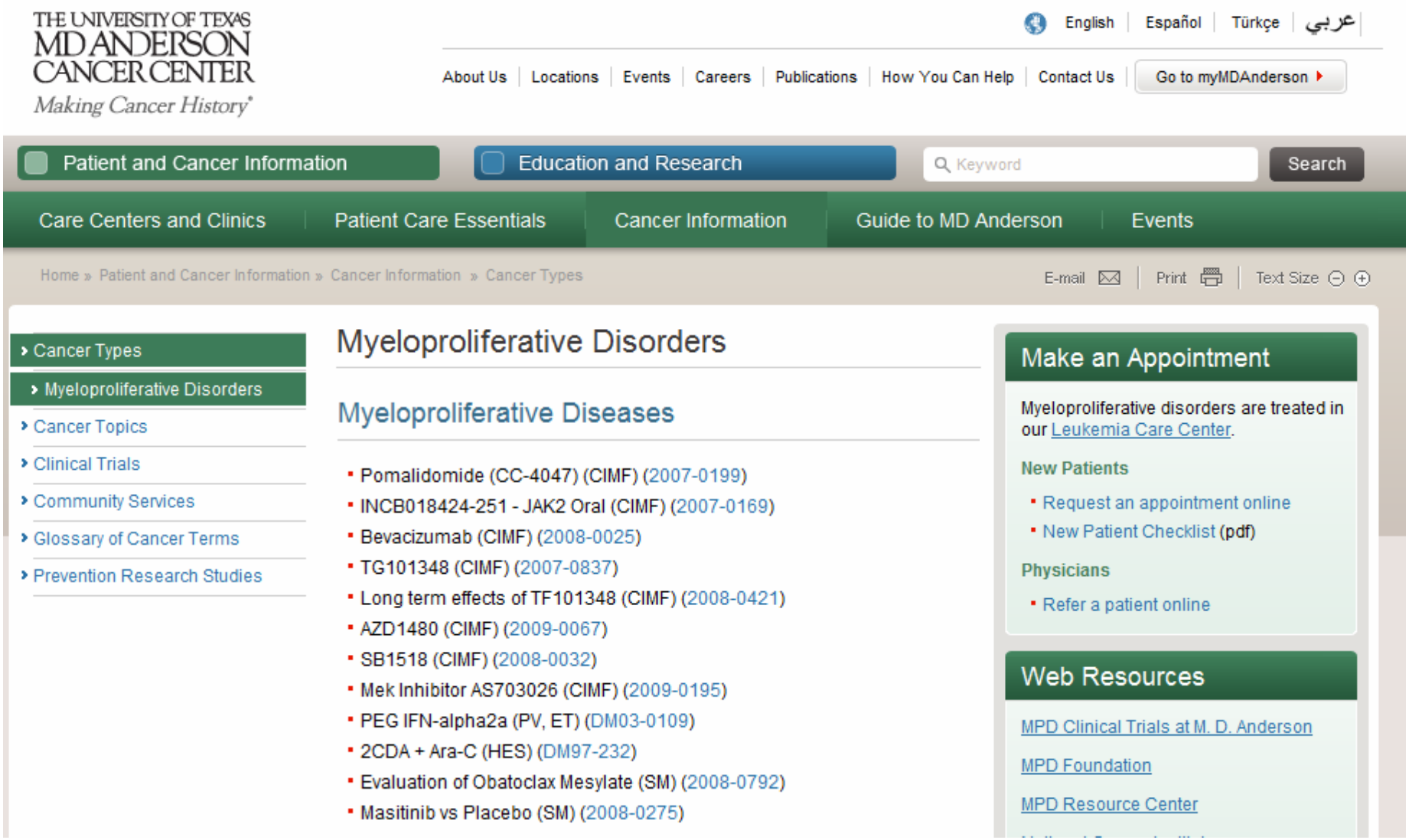
	Anemia	*Splenomegaly*	*Constitutional symptoms*	*Pruritus*	*⇓JAK2 burden*	*Myeloproliferation*	*Reference*
INCB018424	<10%	X	X	X	10%	X	Verstovsek *et al.*[93]
CEP-701	<10%	X	X	—	Not reported	X	Verstovsek *et al.*[96]
XL019	—	X	X	X	10-20%	X	Shah *et al.*[95]
TG101348	—	X	X	X	Not reported	X	Pardanani *et al.*[94]
ITF2357	—	X	X	X	8-12%	X	Rambaldi *et al.*[97]

SciBX
Science-Business eXchange

This week in therapeutics

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Cancer				
Cancer	Janus kinase-2 (JAK2; JAK-2)	*In vitro* studies suggest that RNAi knockdown of the V617F mutant of JAK-2 could help treat myeloproliferative disorders. Existing JAK-2 inhibitors target both wild-type JAK-2 and the cancer-causing JAK-2^{V617F} mutant and thus lack specificity for malignant cells. In a cell proliferation assay, small interfering RNA or small hairpin RNA against JAK-2^{V617F} inhibited cell growth. Next steps include testing the siRNAs and shRNAs *in vivo*. At least seven companies have JAK-2 inhibitors in clinical and preclinical development to treat various cancers.	siRNA sequence patented; licensing status undisclosed	Jedidi, A. *et al. Blood*; published online July 9, 2009; doi:10.1182/blood-2008-09-176875 **Contact:** Jean-Luc Villeval, Gustave Roussy Institute, Villejuif, France e-mail: villeval@igr.fr

http://www.nature.com/whalecom0/scibx/journal/v2/n29/pdf/scibx.2009.1140.pdf



Ensayos Clínicos Controlados sobre MPN en MD Anderson al 2009

Más Allá de JAK2 …

Más Allá de JAK2 …

- Desde 2005 se ha planteado que la sola presencia de la mutación de JAK2no bastaría en todos los casos para inducir MPN, de hecho su prevalencia en Mielofibrosis Primaria es baja.
- En 2009, en Leukemia 2009, 1-8, Goldman et cols plantea la sensación de que a pesar del avance que JAK2 representa, no permite mejorar las opciones diagnósticas.

Más Allá de JAK2 …

- En el ‘Educational Program’ del Congreso Europeo de Hematología 2009 (Berlín, 4 a 7 de Junio de 2009), Kralovics et cols plantean que las mutaciones en JAK2 serían el reflejo esperable de una falla en el mecanismo de reparación :
  - La mutación JAK2 V617F no es heredable.
  - Los parientes de primer grado de un paciente con MPN tienen mayor riesgo de tener MPN. En estudios poblacionales hay 2 haplotipos de JAK2 “Wild type”, pero los mutados pertenecen en un 80% a uno de ellos, el menos frecuente. El locus de JAK2 no se correlaciona con la agregación familiar de las MPN (Blood 2003 ; 102:3793-3797).
  - Otras mutaciones de JAK2 se heredan pero son infrecuentes (exon 12)
  - Otras mutaciones como las de MPL (receptor de trombopoietina) son aún más infrecuentes, pero se pueden comportar como autosómicas dominantes si están en la línea germinal (MPL-S505N, familia japonesa).
  - Existe evidencia frecuente de superposición de múltiples mutaciones en pacientes con MPN (ej : JAK2 + MPL), las que matemáticamente no se producen al azar (1 a 3 eventos en 6000000000 habitantes).

Más Allá de JAK2 …

- Lo anterior ha volcado el interés de los investigadores hacia otras mutaciones :
- Las Alteraciones de TET2
- MPL-S505N, encontrada frecuentemente en líneas celulares de ET y PMF
- MPL W515L, que afecta la expresión de pSTAT5, activando la vía JAK-STAT.
- Variantes del receptor del IGF-2.
- Alteraciones de GATA-1.

TET 2

- TET2 es un gen supresor de tumores localizado en la región de “minimal loss-of-heterozygosity” (LOH) del cromosoma 4q24.
- En pacientes con neoplasias mieloides se han encontrado mutaciones inactivantes que preceden y conviven con JAK2V617F (ASH Annu Meet Abstr 2008; 112: lba–lb3).
- Tiene sentido adjudicarle el origen de estas neoplasias?

GATA 1

- GATA-1 se asocia a S310 para promover la activación de STAT5, aumentando la señal de proliferación celular.
- Además, GATA-1 controla la diferenciación de las líneas eritroide, megacariocítica, mastocitoide y eosinofílica según la concentración disponible.
- La concentración de GATA-1 depende de las secuencias regulatorias específicas en el Locus de *GATA-1*. (Ann N Y Acad Sci. 2005 Jun;1044:142-58).

GATA 1

- Desde 2006 se ha reportado un rol en la supresión de la diferenciación mieloide (Blood. 2006 Jan 1;107(1):87-97).
- Se ha reportado su asociación con otras mutaciones en los Sd Mieloproliferativos asociados a la Trisomía 21 o Sd de Down.
- Se plantea que podría tener un rol en el desarrollo de la mielofibrosis y en explicar la transformación entre estas MPN.

¿ Tengo menos dudas ahora ?

No, pero entiendo un poco más …

Oncología falp
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Gracias …